Unravelling the epidemiology of norovirus outbreaks in hospitals.

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Contents

Abstract

Norovirus is the commonest cause of outbreaks of gastrointestinal disease in the U.K. Most reported outbreaks occur in health care settings, such as hospitals and nursing homes, and can cause severe disruption through ward closures, cancelled operations and staff sickness. Previous studies estimated these outbreaks cost the NHS around £115 million a year.

Despite previous studies some questions remain. What is the burden of norovirus in hospitals - how many outbreaks occur and how many people are hospitalised each year as a result of norovirus infection? Do published reports of outbreaks provide evidence of what works in infection control? Can the factors facilitating norovirus transmission during outbreaks in hospitals be identified? These questions were answered through a series of inter-linked studies that explored mortality, morbidity, transmission pathways and aspects of infection control.

The introduction of a new surveillance system provided greater insights into the heavy burden that norovirus imposes on English hospitals. In the years 2009-2011, 3,980 reports of outbreaks of suspected and confirmed norovirus were received. There was little difference in the epidemiology of outbreaks from one season to the next. On average outbreaks were associated with 13,000 patients and 3,400 staff becoming ill, 8,900 days of ward closure and the loss of over 15,500 bed-days annually.

Analysis of mortality data demonstrated a clear association between norovirus infection and mortality in the elderly (65 years and over) with an estimated 80 deaths per year in this age group. The number of deaths increased in years where norovirus activity was higher but this was not associated with increased pathogenicity of the virus. Norovirus was the only pathogen that had a significant association with mortality in the regression models.

Modeling of routine hospital admission data demonstrates that norovirus accounted for around 3,000 norovirus admissions a year to English hospitals, two thirds of which were in the elderly.

A review of published papers did not provide clear evidence for the effectiveness of infection control measures. However, this was largely because the reporting of outbreaks was poor and that the introduction of more rigorous reporting protocols would improve this.

Analysis of 3,500 outbreaks of norovirus demonstrated that closing a ward or bay promptly (within three days of the first person becoming ill) is beneficial. The duration of outbreak, the total duration of disruption were shorter, and fewer patients overall were affected, if closure occurred promptly. When closure occurred 7 or more days after the first onset date outbreaks were twice as long as those where closure was prompt. The duration of outbreak was also increased by ward size and in outbreaks occurring in winter time. Outbreaks were longer if they occurred on care of the elderly wards. A strategy of prompt closure is beneficial, particularly in larger wards and during winter time.

The time between the first two cases of each outbreak was used to estimate the serial interval for norovirus in a hospital setting and was estimated to be 1.86 days. This distribution and dates of illness onset were used to calculate epidemic trees for each outbreak. A permutation test found strong evidence that proximity was a significant driver of outbreaks ($p < 0.001$). Patients occupying the same bay as patients with symptomatic norovirus infection are at increased risk of becoming infected by these patients compared with patients elsewhere in the same ward.

In summary, there is a demonstrable association with mortality in older people, and around 3,000 admissions to hospital each year. Over 3,900 outbreaks were reported in three years (2009-2011). On average 13,000 patients were affected each year leading to 8,900 days of ward closures. Vomiting appears to be an important driver of outbreaks. Acting quickly by closing affected areas appears to be beneficial in controlling outbreaks caused by norovirus. This is especially the case in larger wards during the winter.

Chapter 1 Introduction

Burden of gastrointestinal disease

Diarrhoeal disease is recognised as one of the leading causes of morbidity and mortality globally [1,2]. The burden is greatest in the developing world, and particularly in children aged less than five years. Whilst there are accepted difficulties in obtaining accurate figures on the burden of disease in developing countries [1] reviews of studies have consistently found similar results [1,2]. In a review by Kosek [1], morbidity from diarrhoeal disease had remained largely unchanged over the last 40 years and children aged under five have 3.2 episodes of diarrhoeal disease each year. Mortality from diarrhoeal causes in children has declined from around 5 million deaths around twenty years ago to 1.5 million in 2004 [3] to around three quarters of a million (0.5 – 1.1 million) deaths in 2010 [4]. Relatively few pathogens cause the majority of acute childhood diarrhoea in the developing world [3]. The Global Enteric Multicenter Study (GEMS) [5,6], a large prospective study carried out in four African and three Asian countries, identified rotavirus as the leading cause of moderate to severe diarrhoea in children aged under five years in developing countries.

Mortality from gastrointestinal disease in developed countries is much lower because of better sanitation, access to medical services and higher nutritional standards in these countries. However, it is still a considerable cause of morbidity and the contribution of viral pathogens as a cause of gastrointestinal disease is much higher in developed countries [7]. Some similarities exist, for example, in developed countries rotavirus is an important pathogen in children. It has been estimated that almost 50 per cent of hospitalisations in children aged under five years for infectious gastrointestinal infections and around 29 percent of all G.P. consultations in that age group [8,9]. The introduction of a vaccine for rotavirus has the potential to substantially reduce mortality and morbidity in children under five. For example, introducing the rotavirus vaccine in the United States has led to a

reduction in the incidence of rotavirus in children under five; however, norovirus is now the leading cause of diarrhoea identified in this age group in clinical settings [10].

In the United States it is estimated that around 23 million episodes of norovirus infections occur [11] (although later estimates have put this figure at 5.5 million [12]), and a little more than 600,000 hospitalisations each year are attributed to viral gastroenteritis [13].

In a study of Infectious Intestinal Diseases (IID), carried out in the mid 1990's in England, it was estimated that one in five people each year suffer from infectious intestinal disease of which viral pathogens are the largest contributor [14,15]. In a second study of IID in 2006 norovirus remained the largest cause of IID in the U.K. [16] In an analysis of data gathered by the Public Health England (formerly the Health Protection Agency), 50 percent of outbreaks of infectious intestinal disease in England were due to norovirus [17,18] and the picture is similar in other parts of Europe [19,20] and Australia [21].

History of viral gastrointestinal disease

In 1929 Zahorsky [22] described a condition for which he proposed the name of 'winter vomiting disease'. He had observed epidemics of gastrointestinal disease over the previous 30 winters. Typically, illness started with an alarming onset of vomiting associated with diarrhoea, and sometimes low-grade fever. The symptoms were consistent with the illness currently ascribed to viral gastroenteritis infection today, although he did not feel that it was true enteritis.

The disease appeared to be self-limiting, usually resolved in two or three days, and with no apparent long-term consequences. Perhaps the one major observation of note was that Zahorsky stated that infections in adults and older children were only occasionally observed and in a milder form. Given that norovirus affects people of all ages this may suggest that the disease he described was more likely to be sapovirus or rotavirus rather than norovirus. However, without the benefit of modern day diagnostics one can only speculate. Other descriptions of clear seasonal increases in gastrointestinal infections have been published,

for example, in England reports of epidemics occurring in 1936 [23] and in 1953 in Skipton, Yorkshire [24] and from a survey in Cleveland Ohio, U.S.A. in the 1950's [25]. Whether any of these epidemics truly were due to viral causes will never be known as there were, at that time, no means to detect viruses in stool or other samples. However, the characteristics of the disease in various early descriptions are highly suggestive of a viral gastroenteritis. The only valid conclusion at the time is that these events were due to non-bacterial causes, as bacteria were not detected in patient's stool samples. There is one outbreak that might be attributed to norovirus even earlier than this. In 1893 an epidemic occurred in a workhouse in Greenwich. The original cause was thought to be cholera but this could not be proven. It was, therefore, proposed that "a theory of gastroenteric influenza might be found to explain the outbreak" [26]. This outbreak was reported in several newspapers with over 200 inmates affected and nine deaths in elderly inmates. The description of the outbreak was of a sudden onset of stomach cramps with diarrhoea and sickness. The deaths were all in elderly patients aged 64 to 92 years.

Challenge studies

In order to test the infectivity of the unknown pathogen human volunteers were recruited who swallowed inocula made from throat washings and stool samples taken from ill individuals [27]. Two experiments were carried out; one with unfiltered samples and the second with filtered samples. After swallowing unfiltered samples volunteers became ill with the same symptoms as those from whom the original samples were taken. Filtered samples, to remove bacterial pathogens, were administered to further volunteers. The volunteers who became ill did so, on average, within three days. What this study showed was the pathogen was not bacterial nor, therefore, was it likely to be from a toxin produced by bacteria. Filtered inocula from samples from the first volunteers were then given to other volunteers who also subsequently became ill.

Discovering viral pathogens in gastrointestinal disease

In 1968 a large outbreak occurred in a school in Norwalk, Ohio, U.S.A. [28] The outbreak was characterised by sudden onset of vomiting and diarrhoea and the attack rates in the school children and staff were high. Furthermore, the families of those affected at the school were also subject to high secondary attack rates [28]. Researchers used frozen samples from this outbreak in more volunteer challenge studies [29]. This study again showed serial infection in groups of volunteers and with high attack rates, but moreover, both clinical manifestations occurred, vomiting with and without diarrhoea and diarrhoea without vomiting. This was an important finding because until then medical text books still referred independently to non-bacterial diarrhoea and winter vomiting disease [29] as though the two were distinct illnesses. The challenge studies of Adler *et al* [28] showed that an infectious agent was capable of producing both syndromes. Because the attack rate was so high, and the volunteers were adults, this was considered to be evidence that immunity to the pathogen was not present in the general population [28]. The samples were also used to try to induce disease in animals, including primates, but no illness was observed, indicating that this was a pathogen exclusive to humans [28-30].

Virus detection

Perhaps the most important finding from the Norwalk outbreak was the visualisation, in 1972, of virus particles in the samples of the challenge volunteers [31]. Kapikian *et al* used a technique that had previously been successful in identifying other viruses, immune electron microscopy, on the volunteer's samples and obtained the first electron micrograph image of the aetiological agent responsible for viral gastroenteritis. This technique uses convalescent sera added to the specimens causing the virus particles to clump together, and thus increased the ability to detect them. At this time the virus was classified as a small round structured virus (SRSV) [32].

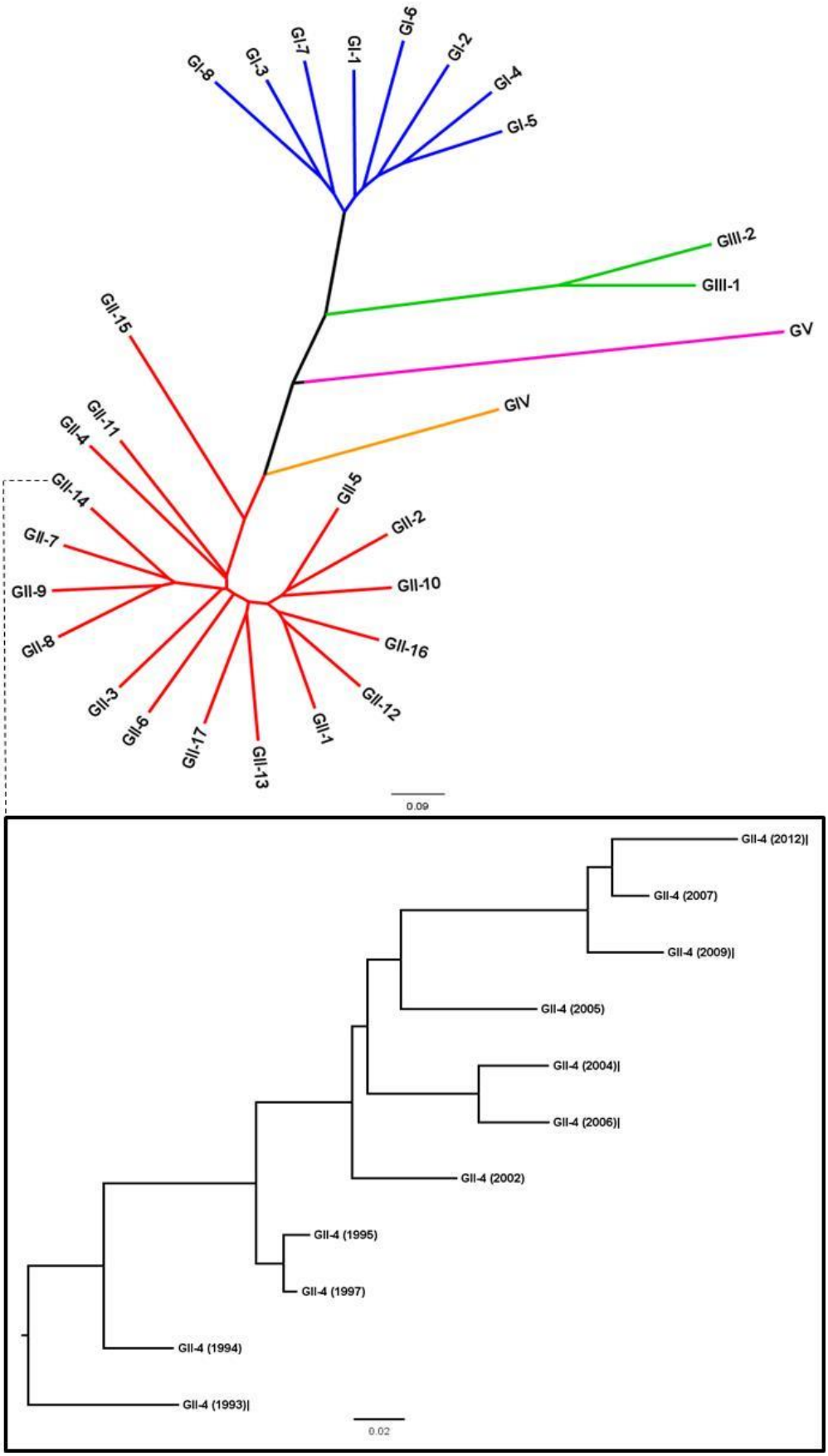
For many years electron microscopy was the only method for diagnosing human calicivirus [33] and classification was based on morphology (the outer shape) [30,34] the distinctive cup like

shape gave rise to the name calicivirus [35,36]. Electron microscopy is an insensitive technique that requires recent samples containing high numbers of virus [30,32-34,37-39]. In 1990 genetic information about the virus led to the classification of SRSV as a member of the caliciviridae family [40-43]. No tissue culture method for human caliciviruses has been developed successfully [30,35,44]. Typing is based on analysis of the virus genome (analysis of the amino acid sequences within the capsid) [44]. Caliciviruses are grouped into five genera [45] two of which are human pathogens and are divided into two based on the prototype strains with classic human calicivirus, now known as sapovirus, and Norwalk-like viruses, which are now known as norovirus. The other viruses (lagovirus, vesivirus, and nebovirus) do not infect humans. Currently norovirus is further divided into five genogroups of which three (I, II, and IV) affect humans and III and V affect only animals [44,46]. Each of the genogroups is further subdivided into a number of genotypes. As yet there is no internationally agreed strain nomenclature or typing scheme [44]. Recently a sixth genogroup has been proposed but there is as yet no international consensus upon this [47].

Diversity of Norovirus

Modern techniques such as reverse transcriptase polymerase chain reaction (RT-PCR) make it possible to detect virus much more easily in human samples (stool and vomit) [48-50] and from the environment. Application of these techniques has shown that there is a wide diversity of norovirus strains [40-43,51-56]. Figure 1 shows the relationship of the different strains. Genogroup I (shown in blue) contains the prototype strain Norwalk (genotype I.1). Genogroup II (shown in red) contains the most commonly identified strain in outbreaks, particularly in healthcare settings (genotype II.4). The continuing evolution of this particular genotype is illustrated in the square box.

Figure 1: Phylogram showing distribution of norovirus genogroups (courtesy of Dr David James Allen from the Virus Reference Department, Public Health England)



Virus diversity is driven by two mechanisms; firstly the virus alters via genetic drift, whereby replication errors creep in [46,57,58]. The virus genome consists of a single strand of positive sense RNA, and lacks the error checking mechanism associated with DNA replication. Point mutations can occur during virus replication [46,57,58]. Secondly, recombination of viral RNA can occur. This happens when a cell is infected with more than one strain at the same time. Evidence suggests that recombination occurs at the break point of open reading frame 1 (ORF1), which codes for a non-structural protein and ORF2 ,which encodes for the virus capsid, however, this does require a high degree of sequence homology, that is at this point the sequences should be almost identical [59-61]. Mostly this occurs among viruses of the same genogroup, and can involve viruses with different genotypes. In this case new variants can emerge as a combination of the two leading to further complications in classification. Analysis of viruses causing outbreaks identifies one particular genotype (genotype II.4) as the predominant cause [33]. In a recent study [53], where a number samples from outbreaks at the beginning, middle and end of the outbreak season, were sequenced it was shown that at the beginning of the season i.e. Late autumn early winter, several different genotypes of norovirus were found to be co-circulating. As the year progressed, certain genotypes began to predominate, mainly GGII.4.

Genetic detection techniques are quicker and allow laboratories to analyse many more specimens than traditional methods, but are not problem-free. In a large study to estimate the incidence and prevalence of infectious intestinal diseases (IID) in England no pathogen was detected in 49 percent of faecal samples [48]. In this study EM was the standard technique for diagnosis. A more recent analysis using RT-PCR on over 4,600 archived samples from the original study increased the detection rate of pathogens from 53 percent to 75 percent overall [48]. In 2,400 archived samples from cases, norovirus was detected in 36 percent of specimens compared with 6.4 percent in the original analysis using electron microscopy alone [48]. Furthermore, in 16 percent of samples from healthy controls it was possible to detect norovirus. Detecting pathogens from people who are not ill (or from

environmental samples), and the increased sensitivity of molecular methods in detecting virus in cases, prompts two important questions. First can we be sure that the virus detected in the stools of symptomatic people is actually causing disease? Detecting virus, either in stool samples or environmental samples, cannot distinguish between intact or damaged virus [62]. Secondly, is asymptomatic carriage an important factor in transmission, or simply a marker of recent infection? In the absence of a culture method, these questions are difficult to answer [63]. Studies looking at viral load in samples may be useful for greater understanding of the question of likelihood of cause of illness [48] and more recent work looking at the cycle threshold (Ct) value in conjunction with positive results suggests that these issues may be resolvable because the study demonstrated that lower Ct values indicated greater viral load in the stool sample [64]. Although there were still some reservations that this might not apply to all genogroups (particularly those rarely seen such as GII.7 or GII.8) the results were promising for the most common circulating strains.

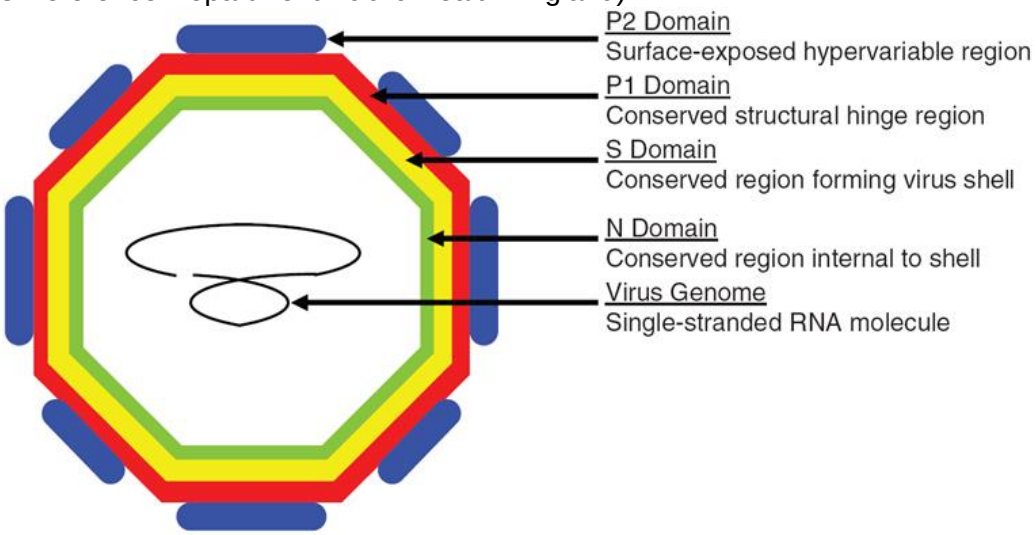
Susceptibility to infection

The volunteer challenge studies showed that some people seemed resistant to infections despite several challenges, while others repeatedly became infected [46,65,66]. This could suggest a genetic resistance to infection. Recently it has been proposed that host factors play a part in the susceptibility to infection. Different blood groupings and carbohydrate secretor status, those who do not exhibit a particular epitope on gut epithelial cells (non-secretors), might be less prone to infection, or even resistant to it [67-73]. There is further evidence that the histo-blood group antigen binding relationship might be strain specific [71] and that noroviruses of the genotype II.4 (Lordsdale strains) are capable of infecting all people regardless of their blood group [74,75] . Therefore, the resistance to infection might be limited to only genogroup I strains. The challenge studies also revealed that some of the study participants did not become ill after a second challenge but were on subsequent challenges. This suggests that infection provides immunity for a short period of time, but this immunity wanes. It seems as though there are at least two mechanisms driving change in

the genetic structure of norovirus but how this interacts with host immunity or susceptibility to infection is not fully understood.

Recently research suggests that changes in the structure of the protruding (P) domain (see figures 2 and 3), the part of the virus most likely to come into contact with the immune system, coincided with the timing of higher than usual seasonal activity [59,76].

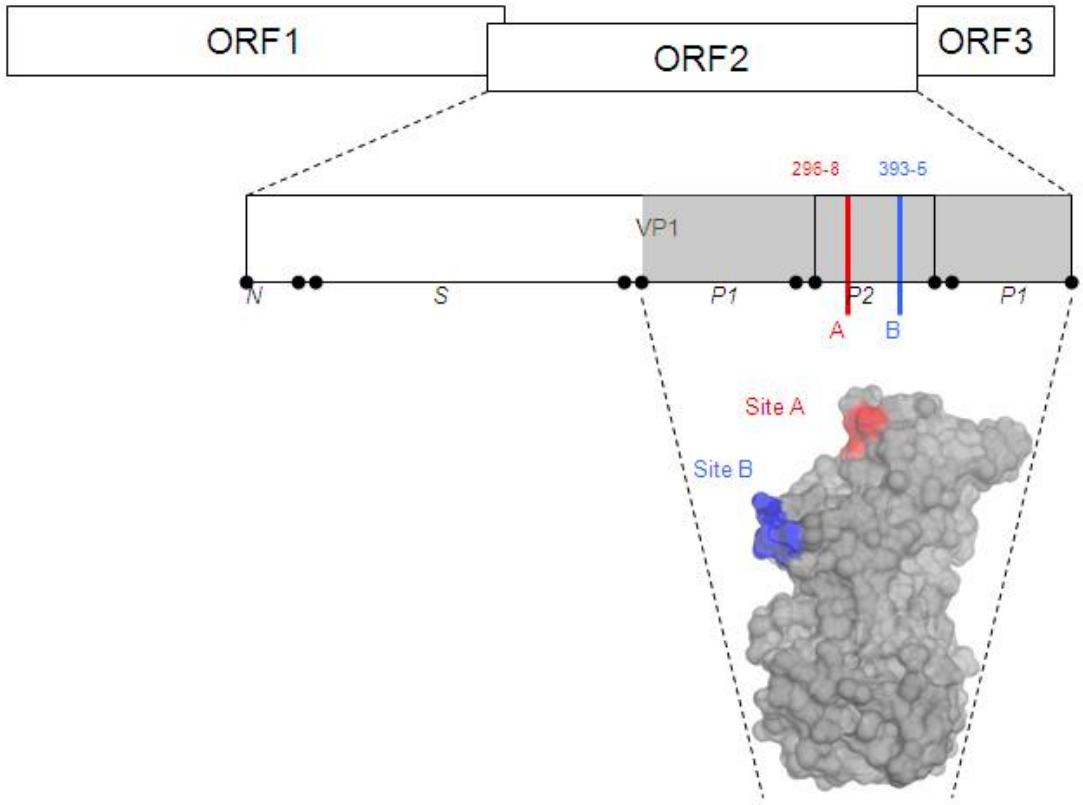
Figure 2 Schematic of the general structure of norovirus (courtesy of Dr David Allen Virus Reference Department Public Health England)



This part of the virus protrudes above the capsid and is assumed to be the part of the virus that binds to receptors on the epithelial wall of the intestine [35,59,77,78]. This region of the virus is referred to as hypervariable because it is subject to rapid changes in the amino acid sequence [59]. This suggests an interaction between the host immune system and changes that occur in the virus acting as a selection mechanism for the evolution of new virus variants. Alterations in the amino acid sequence, whether point mutations or through recombination, might create structural changes in proteins that are beneficial to the survival and transmissibility of the virus. Changes that alter the external shape at points where antibodies might bind to would lead to creating antibody escape mutants [59,79,80]. Two sites have been identified (see figure 3) where such changes occurred and this coincided with high seasonal activity [59,81]. If this occurs then an increase in the susceptible population will occur and large numbers of infections and outbreaks can result. It is clear that new strains

emerge from time to time and coincided with periods of high norovirus activity [82,83]. In 2002 when a new variant of the genotype II.4 strain emerged there was unusual, off seasonal spring and summertime activity of norovirus [83]. Similarly in 2006 another new variant of the genotype II.4 strain emerged globally [82] and this variant was associated with a number of outbreaks especially on cruise-ships, most of which happened in early summer [84,85]. This association is by no means straightforward. In late 2012 it was widely reported in a number of countries that norovirus activity increased by around a month earlier than normal [86]. Moreover, this increase appeared to be associated with a newly emergent GII.4 strain labelled Sydney2012 [86,87]. When this was first recognised there were warnings that this might lead to a particularly bad norovirus season.

Figure 3. Structure of the P2 domain showing two sites believed to be associated with antibody binding, changes at these sites coincided with high seasonal norovirus activity (courtesy of Dr David Allen VRD Public Health England)



There is now some evidence which suggests certain drug treatments can increase individual susceptibility to norovirus infections. Studies on Gnotobiotic pigs showed increased human

norovirus replication in-vitro and increased infectivity in pigs when they were treated with statins [88]. Furthermore, in a cohort study of people affected by norovirus on a pilgrimage showed an increased risk of mortality if they were on statins [89]. This might have implications, particularly in the developed world. If the use of statins increases it could increase the number of people who might possibly suffer more severe disease.

Modes of transmission

The virus can be detected from contaminated surfaces for some time after contamination [63,90-92]. This increases the risk of transferring virus to susceptible people who later have direct contact with those surfaces, or, if that surface is a food, people who consume the contaminated foodstuff. The infectious dose is believed to be very low. As few as 10-100 virions may cause illness [65,93] with one modelling study suggesting that norovirus is the most infectious virus studied to date [94]. This, and the lack of long term immunity to disease [95,96], creates the opportunity for the virus to cause explosive outbreaks. There are numerous reports of outbreaks occurring in settings such as cruise-ships [97-107] where people are in close contact. Some cruise ship outbreaks recur for several voyages, despite thorough cleaning of the ship between voyages following an outbreak, highlighting the difficulty in removing norovirus from the environment [98,99]. Outbreaks have also occurred on military ships [42,108,109] and in other military settings, adversely affecting the ability for effective military operations [108,110-113]. Outbreaks are often seen as a result of secondary person to person spread in these settings. Contaminated surfaces (fomites) can transmit virus to other people who touch them and hand to mouth transfer can lead to the virus being swallowed [114]. A protracted outbreak occurred in a hotel in which successive guests experienced norovirus outbreaks. Even after closing the hotel for one week and deep cleaning, further recurrent outbreaks occurred [63]. There is even one documented case of two maintenance workers being infected after replacing carpet 12 days after the end of an outbreak with no other reason for their illness other than the exposure to the carpet [90]. This suggests that the

viruses can resist commonly used chemicals and persist in the environment for long enough afterwards to infect the new passengers or guests.

Contaminated hands can transfer norovirus onto several surfaces and removal of contamination needs to be carried out carefully. Even after cleaning surfaces, soiled with faecal matter, with hypochlorite solutions norovirus could be detected on almost a third of the surfaces tested [115]. Furthermore, the cleaning cloth was shown to transfer virus between surfaces and the hand [115]. Surfaces might become contaminated either from the spread of direct contact with soiled hands or from aerosolised particles from vomit, and even from toilets which have been flushed after use by someone suffering a diarrhoeal episode [116].

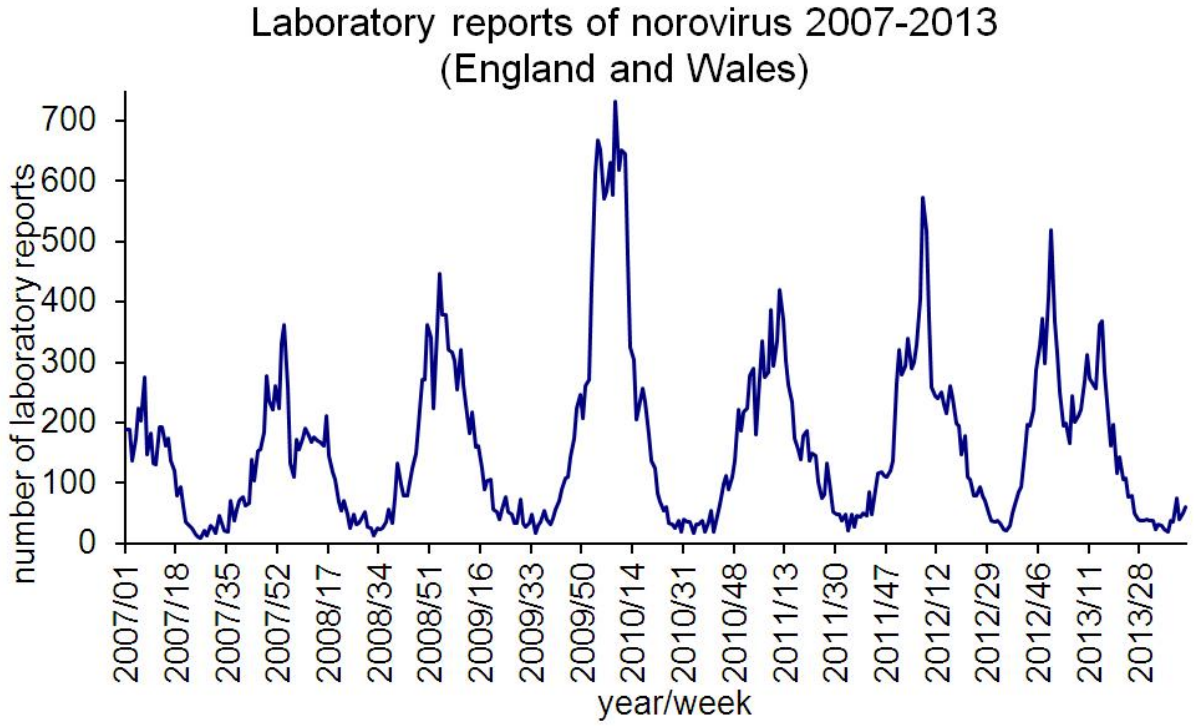
Other studies have shown that vomiting is an important driver of secondary infection. Outbreaks that occurred in a restaurant (but not due to a food borne source) [117], and a concert theatre [118] showed that the attack rates were higher for those in close proximity to the person who first vomited, suggesting that virus can drift in the air on aerosolised particles and is then ingested by people even some distance away. Infections from eating food contaminated either at its source or by infectious food handlers [42,119-125] have resulted in large outbreaks, sometimes occurring in multiple countries [126-133]. Oysters are often cultivated in coastal regions, which can become contaminated by sewage [127,132,134]. Depuration of oysters to remove bacteria is ineffective at removing norovirus contamination [135-139]. A recent study in the UK suggested that over 70 percent of oysters are contaminated with norovirus and the level of contamination detected increased during the winter months [139]**.** Other foods such as frozen raspberries [140,141] have been associated with international outbreaks. Bakery products, contaminated by a symptomatic food preparer (one of which led to an estimated 3,000 people becoming infected) [142,143], and consumption of contaminated water [144-148] are also well documented routes of infection.

Norovirus burden of illness

Much of the disease burden associated with norovirus in the community is hidden from healthcare systems, and hence public health surveillance systems, because it is generally

mild self-limiting illness and people recover before they might consult a healthcare professional. Estimates from cohort studies [14,15,19] (IID1, IID2 and Sensor) have shown that only a small proportion of people infected come into contact with medical services. In the U.K. this under ascertainment is estimated to be around 1 laboratory reported case for every 288 cases in the community [14]. Laboratory reporting exhibits a strong seasonal trend with increases occurring in the winter months. However, this seasonal increase is not uniform and, as has been mentioned above, some seasons are more pronounced than others (see figure 4).

Figure 4 norovirus laboratory reports by year and week (data from Public Health England).



Nosocomial outbreaks and Illness severity

The high seasonal activity characteristic of norovirus activity [149-151] is especially noted in health care settings [152-155]. The commonest reported settings for these outbreaks are in hospitals and nursing homes [18,57,100,154,156-158].

In terms of public health burden, outbreaks in hospitals often lead to serious operational difficulties with wards closed to new admissions, operations cancelled, considerable staff

sickness absence, and in the case of nosocomial infections, increased length of stay for patients. Lopman *et al* [159] estimated that nosocomial outbreaks of gastrointestinal infections cost the NHS around £115 million in 2002-2003. A study determining the cost of nosocomial infections at the same time estimated that the most costly was urinary tract infections at £124 million [160] meaning that gastrointestinal disease was a close second. The length of outbreaks in hospitals may be adversely affected if affected wards are not closed promptly [159].

Infection often begins with sudden and projectile vomiting, which may be associated with watery diarrhoea, nausea, headache, low grade fever and sometimes abdominal cramps may also occur [32,161,162]. Norovirus infection is generally considered a mild disease and most people recover after only one or two days with no long lasting effects [30,157,162]. More recently there is some evidence that suggests that an association between infection with norovirus with exacerbation of irritable bowel syndrome [163,164]. Because only a minority of ill people come into contact with health care services, there are difficulties in assessing the true number of cases. Data based purely on positive laboratory diagnoses grossly underestimates the true number of infections [15,16].

In some circumstances norovirus can have more severe outcomes especially in more vulnerable populations such as the elderly [154,157]. In a large prospective study of outbreaks in nursing homes and hospitals in Avon 2002-2003 Lopman *et al* [157] showed that in hospital outbreaks the median length of illness was longer than that in nursing homes. In another study hospitalised patients with chronic underlying diseases who became infected had severe clinical features [165], and Meakins *et al* [18] demonstrated mortality was higher in hospital outbreaks of gastrointestinal diseases compared with other settings. People in hospital are more vulnerable, as they are already ill and suffering from an illness which is then exacerbated by an acute gastrointestinal infection. Severity of illness may also be related to stress. Military personnel suffered serious acute illness during operations in Afghanistan [110] and some were so ill that they required immediate evacuation to the U.K for

hospitalisation. The presenting symptoms were not immediately recognised as viral gastroenteritis.

Discussion

The information gathered on outbreaks is a reflection of the bias in surveillance systems in place. Outbreaks that occur in enclosed settings are comparatively easy to recognise and investigations triggered.

The seasonal increase and high number of norovirus outbreaks reported are related to the fact that there is no long-term immunity to infection, and the genetic diversity in circulating strains of norovirus. The interaction between the immune system and the virus is not fully understood and the strain variation is likely to be a result of random changes in the genetic structure occurring either by point mutations or through recombination, leading to a strain that has a reproductive advantage. There may also be an environmental component contributing to this seasonality.

From all of this several themes emerge. There are various routes of transmission but there is still some doubt as to which is the most important in passing on the infection. Some studies described outbreaks where environmental contamination was considered to be an important route of infection, but the role of fomites and environmental contamination is still difficult to understand, largely because of the inability to culture the virus and the questions around the meaning of detecting virus genome in samples. In reports of successive outbreaks occurring during cruises the ships were thoroughly cleaned between cruises [103,104,] and yet outbreaks still happened on subsequent voyages. Analysis of outbreaks on cruise ships demonstrated that passengers occupying cabins where people had previously been ill were at higher risk of becoming ill compared with those where the previous occupant was not ill [105].

In health care settings studies reported the highest attack rates for nursing homes and in hospital wards for the elderly, or infirm. In these settings a much higher level of patient contact is required and therefore the potential exists for staff to transfer pathogens to patients, especially if hand hygiene standards lapse. In some of these outbreaks the patients were less mobile so it is possible to accept that this could be the case.

Outbreaks of norovirus in hospital settings cause pressure on staffing levels. If staff become infected the ability to prevent staff movements from one area to another may decrease. The workload for staff is likely to increase because of staff shortages and staff may have to work across infected and non-infected areas [166,167]. Staff might return to work before full recovery and risk spreading infections [167] or even continue to work while ill without taking time off [168].

In terms of infection control, considering all of the above it is difficult to assess which methods are likely to be most effective at breaking the chain of infection. Only one of the recommendations in guidelines on managing outbreaks of norovirus in hospitals by Chadwick *et al* [169], hand washing, is based on evidence strongly supported by experimental epidemiological studies. Other measures are based on expert recommendations based on strongly suggestive evidence or on recommendations where there is no consensus [169.] Only four reviews [170-173] of infection control appear on the Cochrane database, three of which were inconclusive and only one had definitive results showing that hand washing was an effective method for reducing diarrhoeal episodes by 30 percent [171]. A recent review of reported outbreaks of enteric illness, not limited to norovirus, in long-term care facilities, failed to identify suggested recommendations in infection prevention that were evaluated with sufficient rigour [174].

The study in Avon in England found that average length of stay was inversely associated with risk of outbreak incidence, and larger units with higher patient throughput were at an increased risk of experiencing an outbreak. In addition, greater number of beds and geriatric units were identified as risk factors. Having a previous outbreak was initially linked to an increased risk of suffering an outbreak; however, this finding was not significant when taking into account other risk factors such as ward type and patient throughput.

Despite the many studies carried out on norovirus infections and outbreaks there is still little information on the of burden norovirus on the NHS in England. The study by Lopman *et al* provided an estimate in terms of the cost due to staff sickness and lost bed days. It also provided some evidence that it is possible to control outbreaks more quickly if action to close

wards is taken swiftly. However, there is limited data on the number of outbreaks and the impact these have on hospitals in England, both in terms of the number of outbreaks occurring and admissions to hospitals due to norovirus.

A major problem is recognising whether outbreaks are due to re-introduction, from more than one person, or recrudescence, from environmental contamination that has resisted cleaning. One crucial factor in understanding the best way to control outbreaks is to understand more fully the mode of spread through an institution. This can be achieved by clear analysis of outbreaks clearly documenting the chain of transmission.

The challenge then is to undertake systematic and rigorous data collection from hospitals that experience outbreaks of norovirus, and enhanced data collection during a series of outbreaks in hospital settings. Analysis detailing the proximity of those subsequently affected after identification of the index case might lead to an understanding of the relative importance of the different modes of transmission. Improved understanding of the factors driving transmission should inform infection control teams where best to concentrate efforts and prevent on-going transmission.

This poses a number of questions: What is the burden of norovirus in hospitals - both in terms of how many outbreaks occur and how many people are hospitalised each year as a result of norovirus infection? Does the analysis of reported outbreaks provide evidence of what works in infection control? Can the factors facilitating norovirus transmission during outbreaks in hospitals be identified?

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Chapter 2 Overview of Research Methods.

The thesis is presented as a series of manuscripts that address the main research questions. In this chapter the data sources and methods that underpin those research papers are presented in order in which the papers appear.

2.1 Mortality associated with norovirus (chapter 3)

In developed countries the burden of gastrointestinal diseases is largely one of morbidity, however, the risk of diarrhoeal deaths have been shown to be increased in the elderly [1]. Enhanced surveillance, during 2002 and 2003, of gastrointestinal disease outbreaks in hospitals and care homes in one region of England [2], revealed that patients in hospitals fared worse in terms of their recovery, around 10 percent of hospital patients were still ill seven days after their symptoms began. This prompted the question does norovirus contribute to mortality associated with infectious intestinal disease in the elderly? Furthermore, given that norovirus activity can vary between seasons, because of the emergence of new strains, do some seasons lead to more deaths due to increased pathogenicity associated with this emergence?

2.1.2 Data Sources

Office for National Statistics (ONS) data on mortality

The ONS routinely collects data on all aspects of social life in the United Kingdom, including data on births, deaths and marriages. Data are gathered by ONS on information recorded on death certificates by registrars of births and deaths. Death certificates record up to three direct causes of deaths and an underlying cause. These causes of death are coded by trained coders at ONS and are classified according to the International Classification of Diseases (ICD) as defined by the World Health Organisation (WHO). Public Health England

[Formerly the Health Protection Agency (HPA)] receives data annually on deaths which include any code for infectious diseases.

A subset of this annual dataset was extracted where any of the ICD codes included any code for Infectious intestinal disease (IID), i.e., any contributory cause or underlying cause of death with a code for IID. We also extracted a subset for non-infectious intestinal diseases (Non-IID). The data extracted included only those aged 65 and over for the years 2001-2006 inclusive. We excluded from these subsets any deaths which contained the code for *Clostridium difficile* either as contributory or underlying causes of death.

Table 1. ICD codes and death description used for defining cause of death for infectious and non-infectious intestinal diseases.

ICD Code	Description
A00	Cholera
A01	Typhoid and paratyphoid fevers
A02	Other *Salmonella* infections
A03	Shigellosis
A04	Other bacterial intestinal infections (excludes A047,*Clostridium difficile*)
A05	Other bacterial foodborne intoxications
A06	Amebiasis
A07	Other protozoal intestinal diseases
A08	Rotaviral enteritis
A09	Diarrhea and gastroenteritis of presumed infectious origin
A212*	Pulmonary tularemia
A213*	Gastrointestinal tularemia
B462*	Gastrointestinal mucormycosis
K22*	Other diseases of esophagus
K229	Disease of esophagus, unspecified
K29*	Gastritis and duodenitis
K299	Gastroduodenitis, unspecified
K31*	Other diseases of stomach and duodenum
K319	Disease of stomach and duodenum, unspecified
K521	Toxic gastroenteritis and colitis
K528	Other specified noninfective gastroenteritis and colitis
K529	Noninfective gastroenteritis and colitis, unspecified
K92*	Other diseases of digestive system
K929	Disease of digestive system, unspecified
T47*	Poison agents primarily affecting the gastrointestinal system
T478*	Poisoning by other agents primarily affecting the gastrointestinal system
T479*	Poisoning by agent primarily affecting the gastrointestinal system unspecified
Y53*	Agents primarily affecting the gastrointestinal system
Y538*	Other agents primarily affecting the gastrointestinal system
Y539*	Agent primarily affecting the gastrointestinal system, unspecified

* These codes did not yield any results for use in the dataset.

Laboratory reports from Public Health England

Public Health England routinely collects and collates data on over 3000 pathogens. Data are stored in an electronic database (labbase). Data were extracted from faecal or the lower gastrointestinal tract specimens on positive results for IID pathogens. Samples are taken from a number of sources, people who are ill in the community, either at GP visits, or from people infected during outbreaks of IID, sampled by Environmental Health Officers (EHO) or from patients in hospitals.

Various strategies were employed depending on the nature of the study. Laboratory data were either extracted as weekly or monthly counts of IID for various pathogens, including bacteria, viruses and protozoa.

2.1.3 Statistical methods

Poisson regression

Poisson regression is essentially an extension of generalised linear models and used in analysis of data where the outcome variable is either not normally distributed or are random counts. For example, the number of IID deaths occurring in those aged over 65 in each month exhibited a stochastic pattern. In order to estimate the number of deaths due to IID in those aged over 65 associated to norovirus infection using simple linear regression would not be appropriate. Poisson regression assumes that the logarithm of the estimated value is predicted by a linear combination of its predictors and is often written as:

$$\mathrm{Log}_e(Y) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots \beta_n x_n$$

In the modelling of deaths associated with norovirus the coefficient estimated for each pathogen was multiplied by the number of laboratory reports for that pathogen in that month to give the total number of deaths associated with that pathogen estimated by the model.

In order to assess whether the emergence of a new variant was associated with increased pathogenicity we looked for interaction (effect modification) in the model for the season

2002/2003 (when the new variant emerged). Secondly we looked at the ratio of death reports to laboratory reports in each year.

2.2 Hospital admissions due to norovirus (chapter 4)

The estimates from the Infectious Intestinal Diseases study (IID) suggested that norovirus is largely a hidden problem [3], with only a small fraction of cases contacting medical services. Norovirus can be introduced into the hospital environment through infected staff, patients or visitors. Given the increased awareness of outbreaks of gastrointestinal disease in this setting this prompts the question, how many patients are admitted to hospital as a result of norovirus infection each year?

2.2.1 Data sources

Hospital Episode Statistics (HES)

Hospital Episode Statistics (HES) is a data warehouse, in which all data on a patients hospital stay are recorded. This includes all outpatient, in-patient and accident and emergency (A&E) attendances. Data is collected from all National Health Service (NHS) Trusts. Records contain information on diagnoses, and treatments for all patients. Data on diagnoses are coded using the WHO ICD codes. HES data contains several fields for diagnoses http://www.hscic.gov.uk/hes [4].

Data were extracted on emergency admissions for patients aged 18 years and older whose HES diagnosis contained a primary diagnosis code for IID (ICD codes A00 – A09, codes A02.1, A05.1, A06.1-9 were excluded) plus ICD codes for unspecified gastroenteritis and colitis (K52.9). Any admission where the primary diagnosis was for other typical gastrointestinal diseases such as abdominal pain, nausea and vomiting and dehydration were also extracted if they subsequently contained a code defined above in any of the next three diagnosis fields. Data extracted were from week 27 2000 to week 52 2006.

2.2.2 Statistical methods

Linear regression

In order to estimate the number of admissions associated with norovirus an indirect method using simple linear regression modelling was carried out. This technique predicts the total

number of admissions that are attributable to norovirus by comparing the variation in Hospital Episode Statistic (HES) data with the variation in laboratory data. In its simplest form it is usually written as:

$$Y = \alpha + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \ldots \beta_n x_n$$

Where α and β represent the coefficients or the predictor variables. In the modelling of hospitalisations the weekly counts of HES data were modelled against weekly counts of a number of IID pathogens, and a time variable to account for the changing in diagnostic methods for norovirus in later years. Starting with a full model which included all IID pathogens, any that were not significant in the model were removed from the model in turn, until the best fitting (most parsimonious) model was achieved. These non-significant pathogens then make up the unexplained causes of IID contributing to HES admissions. The estimate in the model gives the predicted number of admissions associated with each pathogen.

Model specifications can be tested using the likelihood ratio test, which is a comparison of the Maximum Likelihood Expectation (MLE) from one mode to the other. The Log likelihood of model A is then compared with the Log likelihood of model B.

2.3 The burden of norovirus outbreaks in hospitals in England (chapter 5)

A review of data from surveillance of gastrointestinal disease outbreaks in hospitals for the years 1992-2000 showed the importance of norovirus as a cause of outbreaks in this setting. Although this surveillance scheme provided the first evidence of the nature of the problem, it was part of a system of surveillance of general outbreaks of gastrointestinal disease.

In January 2009 the Health Protection Agency launched a new national reporting scheme for suspected or confirmed norovirus outbreaks in hospitals. The lead in infection prevention and control was contacted by e-mail and by letter to inform them of the launching of the new scheme. Each Trust was given an individual log in to the website. The system was established to answer questions on the burden of norovirus outbreaks in hospitals in England. Specifically how many outbreaks occur in hospitals in England each year? What impact do these outbreaks have? How long do outbreaks last for? How many patients and staff are affected and how many bed days are lost due to outbreaks of norovirus each year?

2.3.1 Data sources

Data are entered by infection control staff at hospitals onto a secure database via the internet. Guidance is provided on the opening page of the website (see figure 5 a-c below) on definitions of both a case of and an outbreak of norovirus. Up to date data on the situation regarding norovirus activity is provided on this opening page with a graph showing the number of confirmed laboratory reports received at Public Health England.

There are also guidelines on assessing whether an outbreak is caused by norovirus in the absence of laboratory confirmation. These are based on Kaplan's criteria indicated in the box below [5]. Although these criteria have been questioned for their applicability in a hospital setting because the original studies were carried out on healthy populations, [6] one study later suggested that these criteria are still sensitive and specific enough for use in judging whether norovirus is the likely cause of an outbreak of diarrhoea and vomiting [7].

The data entry consists of a single form collecting summary information about outbreaks (see figure 3 below). Data items collected include the number of patients and staff affected, date of onset of first and last person to be ill, whether the outbreaks led to a ward or bay closure, the number of bed days lost due to the outbreak and how many specimens were taken and the number of which were positive. Data items collected are shown in figure 5 below. Data on outbreaks can be entered in real time as they occur and can be updated at any time during the outbreak or after its conclusion.

Figure 5 a opening page of hnors website with link to definitions for guidance.

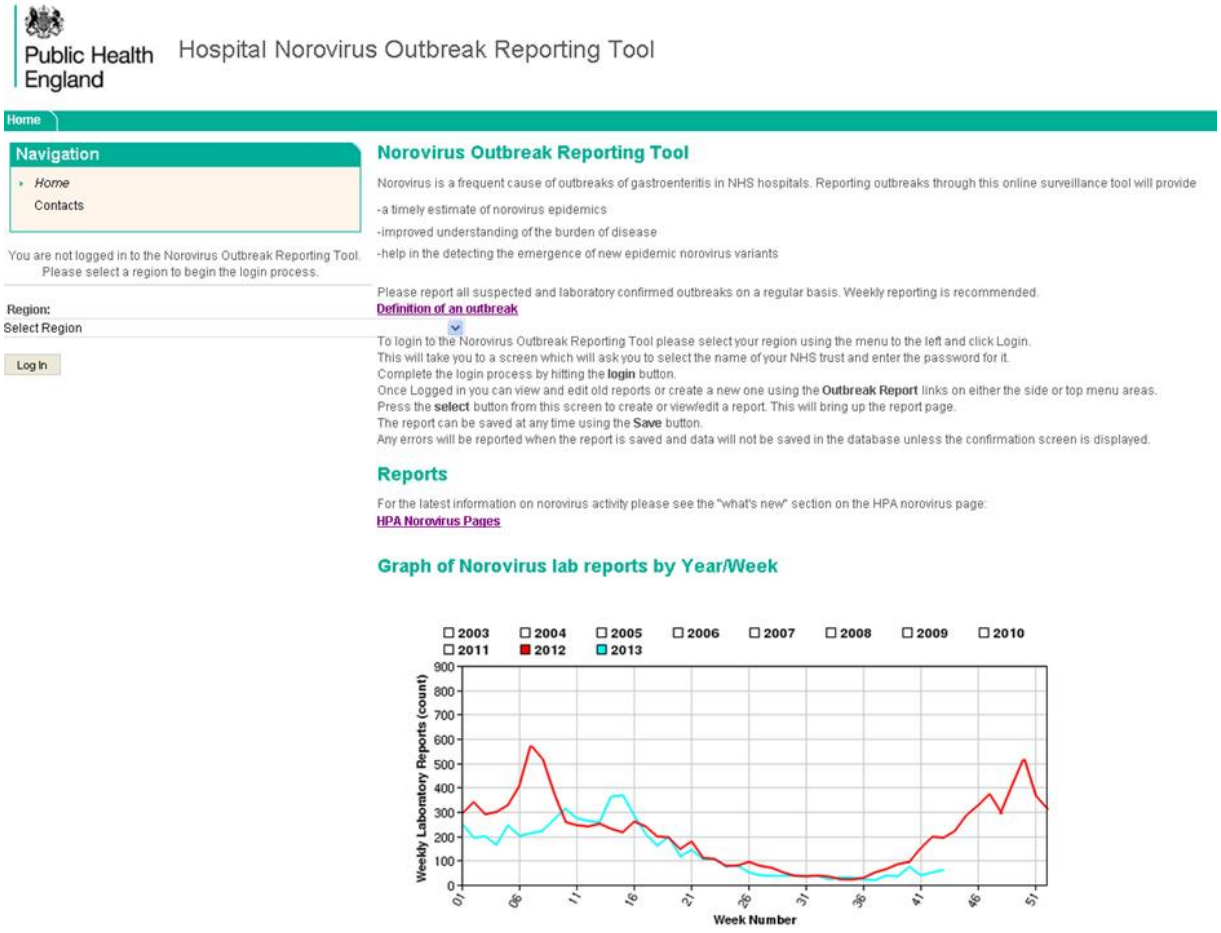
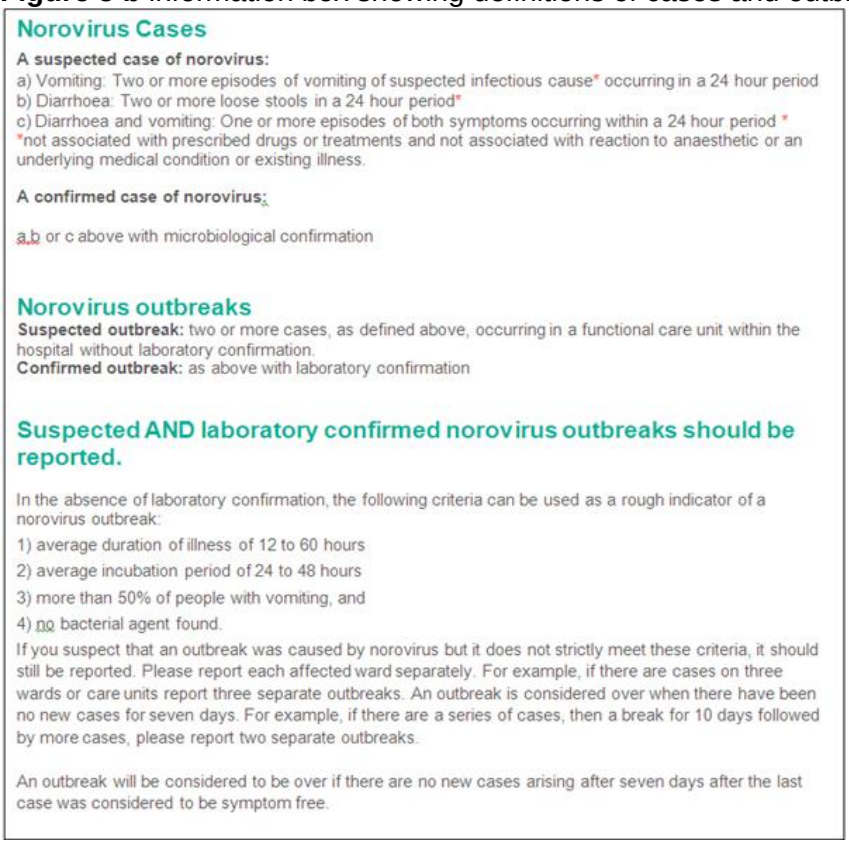


Figure 5 b information box showing definitions of cases and outbreaks of norovirus.



Norovirus Cases

A suspected case of norovirus:

a) Vomiting: Two or more episodes of vomiting of suspected infectious cause* occurring in a 24 hour period
b) Diarrhoea: Two or more loose stools in a 24 hour period*
c) Diarrhoea and vomiting: One or more episodes of both symptoms occurring within a 24 hour period *
*not associated with prescribed drugs or treatments and not associated with reaction to anaesthetic or an underlying medical condition or existing illness.

A confirmed case of norovirus:

a,b or c above with microbiological confirmation

Norovirus outbreaks

Suspected outbreak: two or more cases, as defined above, occurring in a functional care unit within the hospital without laboratory confirmation.
Confirmed outbreak: as above with laboratory confirmation

Suspected AND laboratory confirmed norovirus outbreaks should be reported.

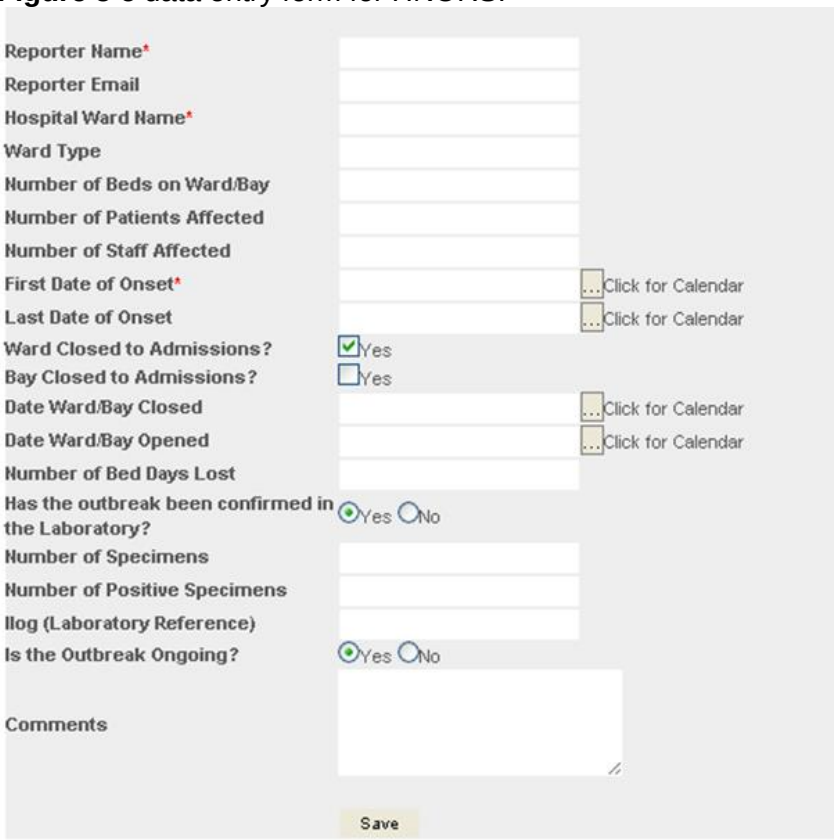
In the absence of laboratory confirmation, the following criteria can be used as a rough indicator of a norovirus outbreak:

1) average duration of illness of 12 to 60 hours
2) average incubation period of 24 to 48 hours
3) more than 50% of people with vomiting, and
4) no bacterial agent found.

If you suspect that an outbreak was caused by norovirus but it does not strictly meet these criteria, it should still be reported. Please report each affected ward separately. For example, if there are cases on three wards or care units report three separate outbreaks. An outbreak is considered over when there have been no new cases for seven days. For example, if there are a series of cases, then a break for 10 days followed by more cases, please report two separate outbreaks.

An outbreak will be considered to be over if there are no new cases arising after seven days after the last case was considered to be symptom free.

Figure 5 c data entry form for HNORS.



Reporter Name*	
Reporter Email	
Hospital Ward Name*	
Ward Type	
Number of Beds on Ward/Bay	
Number of Patients Affected	
Number of Staff Affected	
First Date of Onset*	...Click for Calendar
Last Date of Onset	...Click for Calendar
Ward Closed to Admissions?	☑ Yes
Bay Closed to Admissions?	☐ Yes
Date Ward/Bay Closed	...Click for Calendar
Date Ward/Bay Opened	...Click for Calendar
Number of Bed Days Lost	
Has the outbreak been confirmed in the Laboratory?	◉ Yes ○ No
Number of Specimens	
Number of Positive Specimens	
Ilog (Laboratory Reference)	
Is the Outbreak Ongoing?	◉ Yes ○ No
Comments	

Save

Laboratory data

Public Health England has regional laboratories to which stool specimens are referred from patients who experience diarrhoeal disease in hospital for confirmation of causal pathogen. Data were requested from regional laboratories to report the number of outbreaks for which they had received specimens, with details of the hospitals and wards from which they were obtained, along with the dates of the outbreak.

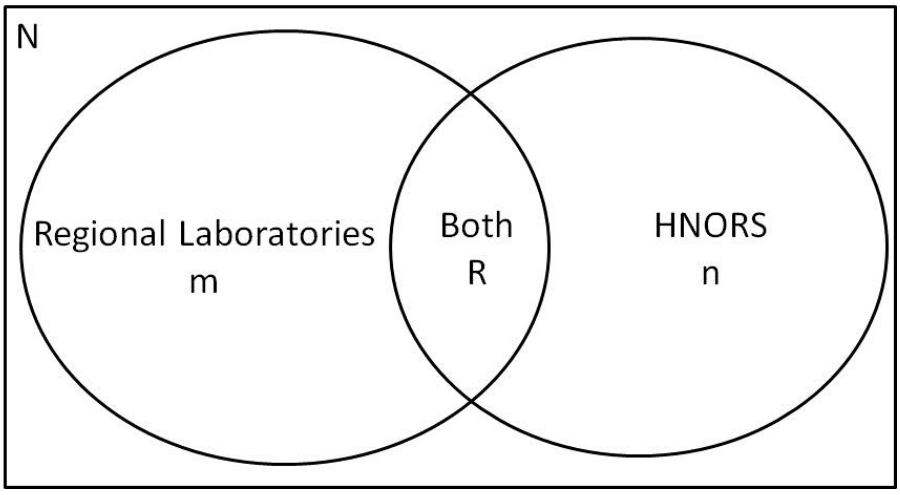
2.3.2 Data analysis

The data from HNORS was analysed to obtain summary statistics, mean median and interquartile ranges for a number of measures. This was carried out using Microsoft Excel

2007 (Microsoft Corporation, USA). The data were compared with those reported in the previous reporting scheme. The data from the reference laboratories were used to assess the level of under ascertainment of outbreak reports to HNORS. A form of capture/recapture analysis was carried out using HNORS data and regional laboratory data as the two samples.

An estimate of the ratio of non-reported outbreaks to reported outbreaks calculated as $N = n*m/R$ where n is the number of HNORS only reported outbreaks m is the number of Regional laboratory only reported outbreaks and R is the number of outbreaks that appeared in both systems, i.e. Matched (see figure 6).

Figure 6 capture/recapture method



Outbreaks were considered to be a match (R) if they (a) occurred in the same Trust and hospital, and (b) where the first date of onset of illness in the reported outbreak and the specimen dates were within 14 days of each other and (c) did not have different ward names. Where the ward name was missing from the laboratory if criteria (a) and (b) were met the outbreaks were still considered a match. This gives a large estimate for R, and therefore a conservative (low) estimate of the total number of outbreaks (N). The reporting ratio was then calculated as (N-n+R)/(n+R).

2.4 Systematic review (chapter 6)

The guidelines for controlling outbreaks of gastrointestinal diseases in hospitals are based on expert opinion. Only one of the recommended measures is based on experimental scientific evidence. A systematic review was conducted to assess the evidence of the effectiveness of infection control measures. The research question posed was, does the published literature provide an evidence base for which measures in infection control are effective in controlling outbreaks of norovirus in closed or semi-enclosed settings?

2.4.1 Methods

Published papers on outbreaks of norovirus in enclosed or semi-enclosed settings were reviewed. Papers were included if they had reported information on attack rates, number at risk and numbers affected. Outbreaks that were reported as foodborne or waterborne were only included if they occurred in enclosed or semi-enclosed settings.

A keyword search was performed for the terms: norovirus, small round structured virus, norwalk virus, SRSV, small round virus, norwalk-like virus, winter vomiting disease, and gastric flu that appeared either in the title or the abstract of the article. The search was performed on pubmed, Medline, Google Scholar, and Embase. All articles had to be in English. All abstracts from the identified articles from the first search were again filtered by searching for the terms: hospital, outbreak, outbreak control, control measure(s), semi-closed environment, semi enclosed environment, nursing home, cruise ship or school.

2.4.2 Data analysis

The data were analysed to assess if any differences could be perceived between outbreaks in different settings and those where infection control measures were implemented compared with those where they were not. The following data items: attack rates; the number of people affected and at risk, case or outbreak definition; whether outbreak control measures were implemented; and claims of effectiveness of interventions were extracted.

Test for heterogeneity in meta-analysis

Meta-analysis is where measures from a number of studies are combined in order to estimate the level of the effect being measured. Often this might be used in assessing a number of studies where the effect of an exposure (e.g. Type of drug, exposure to alcohol) is calculated in each study. These studies can then be pooled to give greater power for estimating the effect. However, there are several problems with this approach, not least being the type of study, whereby observational studies might provide less robust estimates than intervention studies, particularly randomised control studies. Simply pooling the data from a mixture of studies might give a false impression of the true nature of the effect [8]. There is a test of heterogeneity which will test if the effects are different in the different study types. This is essentially a z test to see whether there is a systematic difference in the effect being investigated by study design. If there appears to be a significant difference in the effect according to study design it is unreliable to use a pooled estimate.

Mann-Whitney Rank sum tests were performed to assess any differences between various measures including the length of outbreaks, the number of people affected and attack rates to comparing outbreaks where infection control measures were implemented against those that were not. Rank sum tests are a non-parametric test for a comparison of the distribution of two independent samples. This is analogous to the t-test, and assesses if there is any difference between the distributions of variables between the two groups. The null hypothesis is that there is no difference.

2.5 Does spatial proximity drive norovirus transmission during outbreaks in hospitals? (Chapter 7)

The effectiveness of individual infection control methods is difficult to assess. There is some evidence that vomiting events have been implicated as an important factor in spreading norovirus. Understanding the role spatial proximity could provide insights into improving infection control. This study was aimed at understanding what drives norovirus outbreaks in hospitals. Does proximity of patients to one another have a bearing on the transmission of norovirus? And if so, are there implications for infection control?

The approach for the research in chapter 7 was to obtain data from enhanced surveillance of outbreaks of diarrhoea and vomiting in hospitals. The following describes the data sources and methods used for the study.

2.5.1 Research Design

Enhanced Surveillance of norovirus outbreaks in hospitals

The setting was two acute National Health Services hospitals in major cities - one in the North West of England and one in the Midlands.

2.5.2 Surveillance materials

Population studied

Patients

Any in-patient on any ward within the Trust who has at least one overnight stay.

Case/outbreak

Norovirus infections are common in the population, to the extent that case-based surveillance in the community is impractical. Outbreaks tend to be recognised based on detecting cases clustered in space and time. Cases and outbreaks of norovirus were defined as:-

A case of gastroenteritis (and exclusion criteria)

A) Vomiting: Two or more episodes of vomiting of suspected infectious cause* occurring in a 24 hour period.

B) Diarrhoea: Two or more loose stools in a 24 hour period*

C) Diarrhoea and vomiting: One or more episodes of both symptoms occurring within a 24 hour period *.

*not associated with prescribed drugs or treatments and not associated with reaction to anaesthetic or an underlying medical condition or existing illness.

Outbreak

An outbreak was defined as two or more cases, as defined above, occurring in a functional care unit (ward or bay) within the hospital.

Cases were in-patients who had at least one overnight stay in the hospital at the time of the outbreak.

An outbreak was considered to be over if there were no new cases arising after seven days after the last case was considered to be symptom free.

2.5.3 Reporting

Case report forms (see form 1 below)

Basic demographic data and details of the illness experienced for each person meeting the case definition were completed on the case report form. The first (primary) case arising in the ward/bay was requested to be entered on line one, with subsequent cases' details in order of their occurrence. This provided a line listing of the cases involved in the outbreak (staff and patients)

Reporter's name, the name of the person who completed the form

Name of ward/unit, the name of the ward or bay that the ill patients occupied during the time they were ill during the outbreak.

Contact phone number, telephone number, and extension where the reporter can be contacted.

Reference number of the case, a reference number of the patient purely for data entry and analysis purposes. No names were used in data collection.

Age, the age of the patient at their last birthday.

Date of onset, the date the patient first exhibited symptoms (diarrhoea, vomiting or both) and whether this was morning (12.00 noon or earlier) or afternoon (after 12.00 noon) on that date.

Sample date, the date the patient's sample was taken.

Symptoms, the symptoms exhibited by the patient recorded by ticking the appropriate boxes for diarrhoea, or vomiting or both if both symptoms were experienced.

First symptom free date, the date the case was first free of any diarrhoea or vomiting.

Position, the position in the ward/bay (the bed number and bay occupied by the patient) when they became ill. See ward position layout.

Ward layout diagrams (figure 7)

This was a plan of the wards. Each position on the plan has a bed position and each is numbered. This should be used to indicate on the case report forms the position of each patient on the functional care unit where they were when they first became ill. An example was provided for infection control staff (figure 5)

Outbreak report forms

Summary information on the outbreak was recorded on this form (see form 2 below).

Ward closure, this refers to a ward or part of a ward (such as a bay) where beds were closed to new inpatient admissions for the duration of the outbreak.

Primary case, the first person who becomes ill on a ward. Details of where this person was in the 24 hours prior to the outbreak was also requested. If the person was transferred in to

the ward where they fell ill from another part of the hospital the ward or department that the case was transferred from was requested to be recorded here. In some outbreaks there may be more than one person becoming ill at the same time. In this situation they were considered as co-primary cases and the number of the co-primary cases was requested to be recorded including how many were transferred in to the ward from another part of the hospital.

Form 1. The case report form

Reporter's name: _____ Name of ward/unit: _____

Contact phone number: _____

Case number	Case reference number	Age (in years)	Sex	Date & time of onset	Sample date	Symptoms	First symptom free date	Co-primary?	Bed location at onset of symptoms	Location of primary and co primary cases 24 hrs < onset (specify)*
1[o]			☐M ☐F	☐AM☐PM☐N/K __/__/__	__/__/__	☐D ☐V	__/__/__			☐community ☐other ward
2			☐M ☐F	☐AM☐PM☐N/K __/__/__	__/__/__	☐D ☐V	__/__/__	☐Y		☐community ☐other ward
3			☐M ☐F	☐AM☐PM☐N/K __/__/__	__/__/__	☐D ☐V	__/__/__	☐Y		☐community ☐other ward
4			☐M ☐F	☐AM☐PM☐N/K __/__/__	__/__/__	☐D ☐V	__/__/__	☐Y		☐community ☐other ward
5			☐M ☐F	☐AM☐PM☐N/K __/__/__	__/__/__	☐D ☐V	__/__/__	☐Y		☐community ☐other ward
6			☐M ☐F	☐AM☐PM☐N/K __/__/__	__/__/__	☐D ☐V	__/__/__	☐Y		☐community ☐other ward
7			☐M ☐F	☐AM☐PM☐N/K __/__/__	__/__/__	☐D ☐V	__/__/__	☐Y		☐community ☐other ward
8			☐M ☐F	☐AM☐PM☐N/K __/__/__	__/__/__	☐D ☐V	__/__/__	☐Y		☐community ☐other ward
9			☐M ☐F	☐AM☐PM☐N/K __/__/__	__/__/__	☐D ☐V	__/__/__	☐Y		☐community ☐other ward
10			☐M ☐F	☐AM☐PM☐N/K __/__/__	__/__/__	☐D ☐V	__/__/__	☐Y		☐community ☐other ward

***Location 24 hrs prior to onset ONLY for primary/co-primary cases.**
Please specify if community or enter name of ward

Form 2. The outbreak summary form

Reporter's name:_____ Today's Date: ____/____/_____

Name of ward:_____ No. Of beds in unit _____

Type of ward:_____ No. Of staff in unit: _____

Total affected

Staff: _____ Patients: _____

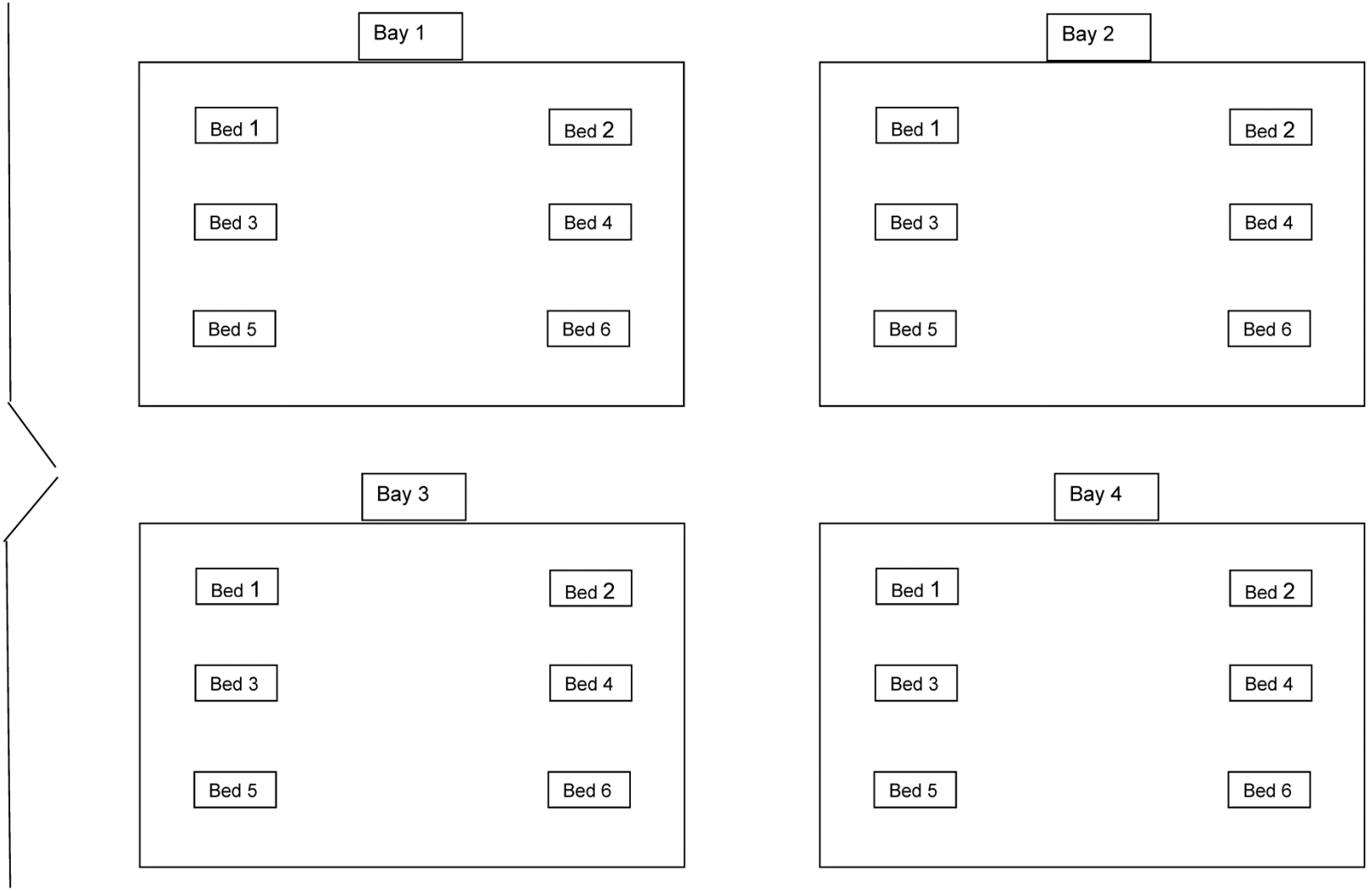
Date of onset of first case __/__/____ Date of onset of last case __/__/____

Which beds remained empty due to bed closures? (use ward layout diagram)

Bed Number												
Days unoccupied due to closure												

Additional comments (external links to other outbreaks)

Figure 7 example ward layout



2.5.4 Statistical analysis

The analysis was based upon calculating chains of transmission. These were based on the onset dates of patients involved in outbreaks of norovirus. The dates of onset allows for the estimation of the probability that one patient affected another for each pair of infected patients. This relies upon estimates of the serial interval. The serial interval was estimated using the distributions of time between onset dates of first and second cases during the observed outbreaks. A 95 percent confidence interval for the serial interval was obtained by bootstrapping (running 1,000 re-samples of the observed serial interval distributions).

The probabilities in each infection tree were summed for patients who share a bay (this was a binary variable 1 for patients sharing a bay and 0 for not). This gave an observed metric for the proximity. The data from each outbreak was then simulated 1,000 times. In each simulation patients were randomly allocated to same or different bay. The proximity metrics for each simulation were summed. This gave an expected distribution of proximity metrics where proximity played no role in spreading disease. A comparison of the observed value with the distribution of permuted values of the proximity metric allows for a two sided hypothesis test of whether transmission is more or less likely to occur in patients sharing a bay. If the observed value fell outside of the simulated values then transmission was less likely (if it falls in the lower tail) or more likely (if in the upper tail) to occur in patients in proximity. Sensitivity analysis was carried out by running models with various estimates of the serial interval.

2.5.5 Data protection

To comply with the data protection act and Caldicott guidelines all case reports were anonymous and no direct identifier was included on the cases report form.

2.5.6 Ethics

The study did not require ethics committee approval. A letter from the appropriate ethics committee is attached in the appendix.

2.6 To close or not to close? Analysis of four years data from national surveillance of norovirus outbreaks in hospitals in England (chapter 8)

The research so far suggests that proximity plays a role in transmission of norovirus. Lopman *et al* had previously demonstrated that there is likely to be a benefit in closing wards quickly after the onset of an outbreak of norovirus (within three days of the first case becoming ill) [9]. A criticism of this analysis arises in the guidelines on managing outbreaks in hospital settings was that in the data from the Lopman study only 7 of the outbreaks closed within this prompt period and at least one of these outbreaks were atypical [10]. The data from the surveillance of outbreaks of norovirus in hospitals, presented in chapter 5, showed that in over 80 percent of outbreaks the wards or bays were closed within three days of the first onset date. Therefore the question is still valid - is prompt closure of an affected ward an effective method of controlling an outbreak?

2.6.1 Data sources

Data were taken from the surveillance of outbreaks of norovirus in hospitals. The duration of outbreaks, disruption, ward closures, the number of patients and staff affected and lost bed days, was compared between outbreaks when closure was prompt (closed within three days) and not prompt (closed after three days).

2.6.2 Statistical methods

The group comparisons were made as a function of the timing of closure. Four groups were created: group1 = prompt closure (within three days of the first onset date), group2 = closure between four and six days, group3 = closed seven or more days, group4 = not closed. Group1 was the baseline group for analysis.

The data were highly right skewed. Non parametric tests (Kruskal-Wallace rank sum tests) were used to estimate whether the median of each outcome measure differed between the four groups.

Quasi-Poisson regression analysis was used to estimate the effect of the timing of ward closure on outcome measures, controlling for time of year (winter/summer) and ward size and ward type (elderly care wards). A major assumption of Poisson regression is that the mean and the variance are equal. Variations on this assumption can lead to over dispersion (variance greater than the mean) or under dispersion (variance less than the mean). Where this assumption is violated it is necessary to modify the regression model, either by using negative binomial, zero inflated or Quasi-Poisson regression models. The results will not affect the estimated value of $\mathrm{Log}_e(Y)$ But will lead to a more robust estimation of the standard errors. The data displayed evidence of over dispersion. Therefore, in this analysis Quasi-Poisson regression was used. As before the regression model took the form:

$$\mathrm{Log}_e(Y) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots \beta_n x_n$$

The estimated outcome (length of closure, patients affected) is calculated by multiplying the each of the exponent terms in the model. This allows each outcome to be estimated depending on whether the outbreak occurred in a particular ward type (elderly care ward) or in winter and by closure group.

And therefore: $Y = \left(e^{\beta 0}\right)\left(e^{\beta 1 x 1}\right)\left(e^{\beta 2 x 2}\right)\left(e^{\beta n x n}\right)$

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Chapter 3. Deaths from Norovirus among the Elderly, England and Wales

Deaths from Norovirus among the Elderly, England and Wales

John P. Harris, W. John Edmunds, Richard Pebody, David W. Brown, and Ben A. Lopman

The number of deaths in England and Wales associated with gastrointestinal pathogens, norovirus in particular, in persons ≥65 years was estimated for 2001–2006. Regression analysis was used to model monthly counts of gastrointestinal pathogens in fecal samples from infected patients against monthly counts of deaths from infectious and noninfectious intestinal diseases. Data came from the Office of National Statistics (death registrations from local registrars) and from the Health Protection Agency (laboratory results). Model results suggest that 20% (13.3%–26.8%) of deaths in persons ≥65 years of age caused by infectious intestinal disease other than *Clostridium difficile* were associated with norovirus infection in this period and that 13% (7.5%–18.5%) of deaths caused by noninfectious intestinal disease were associated with norovirus. An estimated 80 deaths each year in this age group may be associated with norovirus infection.

Estimating the number of deaths associated with infection is challenging. Deaths resulting from infectious diseases tend to be underreported on death certificates (*1*). Similarly, laboratory reports record the pathogens detected but rarely record long-term outcomes, such as death or other sequelae. Routine hospital admissions and discharge data only record deaths that occur in hospital, and coding may not always be complete or accurate, especially if diagnostic results are not available (*2*,*3*).

Norovirus is the most common cause of acute gastrointestinal infections and causes most reported outbreaks of gastrointestinal disease in England and Wales (*4*). Outbreaks occur more often during the winter months of October to March (*5*), but occasionally unexpectedly high activity can occur during the summer months (*6*). To date, no published data estimate the number of deaths from norovirus infections in the United Kingdom. We estimated the number of deaths associated with gastrointestinal pathogens by using previously reported methods (*1*,*2*,*7*–*9*) and, in particular, we estimated the seasonal contribution of norovirus to death in the elderly (≥65 years of age). We also tested the hypothesis that the 2002–03 norovirus season, when a novel strain emerged (*10*), was associated with more pathogenicity than were other norovirus seasons.

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Methods

Data Sources

Laboratory Reports

The Health Protection Agency collects data from laboratories around England and Wales on pathogens identified in fecal samples from infected patients with gastrointestinal symptoms (*11*). Samples come from persons in the community (taken by general practitioners), from persons involved in outbreaks (taken by Environmental Health Officers), and from hospitalized patients. Monthly counts (based on the date the specimen was taken) of positive specimens for January 2001–December 2006 were extracted for those ≥65 years of age. The organisms responsible for gastrointestinal diseases extracted for the analysis were *Salmonella* spp., *Shigella* spp., *Campylobacter* spp., *Escherichia coli* (not Shiga-toxin producing), enteric adenovirus, rotavirus, astrovirus, norovirus, *Cryptosporidium* spp., and *Giardia* spp. All other intestinal parasitic diseases were grouped together as other parasites. All bacterial pathogens were grouped by genera; e.g., all *Campylobacter* spp. were grouped together.

Mortality Statistics

The Office of National Statistics (ONS) compiles mortality statistics based on death registrations from local regis-

trars in England and Wales. Cause-of-death information on death certificates is coded by ONS according to the International Classification of Diseases, 10th revision. Annually, ONS provides HPA with a file of all deaths that mention an infectious disease code. Deaths with a code for an infectious intestinal disease (ID), either as the underlying cause of death or a contributing cause of death, were extracted for 2001–2006 for persons ≥65 years of age (Table 1). We repeated the exercise for deaths that were considered to be caused by noninfectious ID. Deaths with any mention of *Clostridium difficile* were excluded from the analysis.

Table 1. International Classification of Diseases, 10th Revision, codes used for defining deaths from infectious and noninfectious causes, England and Wales, 2001–2006

Code	Diagnosis
A00	Cholera
A01	Typhoid and paratyphoid fevers
A02	Other *Salmonella* infections
A03	Shigellosis
A04	Other bacterial intestinal infections (excludes A047, *Clostridium difficile*)
A05	Other bacterial foodborne intoxications
A06	Amebiasis
A07	Other protozoal intestinal diseases
A08	Rotaviral enteritis
A09	Diarrhea and gastroenteritis of presumed infectious origin
A212*	Pulmonary tularemia
A213*	Gastrointestinal tularemia
B462*	Gastrointestinal mucormycosis
K22*	Other diseases of esophagus
K229	Disease of esophagus, unspecified
K29*	Gastritis and duodenitis
K299	Gastroduodenitis, unspecified
K31*	Other diseases of stomach and duodenum
K319	Disease of stomach and duodenum, unspecified
K521	Toxic gastroenteritis and colitis
K528	Other specified noninfective gastroenteritis and colitis
K529	Noninfective gastroenteritis and colitis, unspecified
K92*	Other diseases of digestive system
K929	Disease of digestive system, unspecified
T47*	Poison agents primarily affecting the gastrointestinal system
T478*	Poisoning by other agents primarily affecting the gastrointestinal system
T479*	Poisoning by agent primarily affecting the gastrointestinal system unspecified
Y53*	Agents primarily affecting the gastrointestinal system
Y538*	Other agents primarily affecting the gastrointestinal system
Y539*	Agent primarily affecting the gastrointestinal system, unspecified

*Although these codes were used in the search, none yielded any results for use in our dataset.

Statistical Analyses

Because most gastrointestinal pathogens are highly seasonal, we estimated the number of gastrointestinal-related deaths by regressing monthly counts of laboratory reports on monthly counts of deaths. As we could not assume monthly counts of deaths to be normally distributed, simple linear regression models were inappropriate. We modeled monthly counts of deaths as a Poisson distribution, which has properties appropriate for analysis of count data. We used generalized linear regression models, which are used to extend simple linear regression to incorporate other distributions, to model monthly deaths as a Poisson-distributed outcome of laboratory reports of gastrointestinal pathogens.

Poisson regression also assumes that the data are not overdispersed (i.e., the variance is equal to the mean). Negative binomial models relax this assumption; we also considered negative binomial models, although they gave no qualitative differences in the results. To estimate the number of deaths that may be attributed to each pathogen, all models were fitted by using STATA 10.0 (*12*).

Our approach assumed a fixed proportion of laboratory reports for each organism to deaths over the period examined. The initial model included all laboratory reports for the extracted organisms as explanatory variables (Table 2). A constant term was included in all models to account for deaths not explained by the seasonal variation in laboratory reports. Because the number of deaths reported in each year (from both infectious and noninfectious ID) exhibited an upward trend during the study period, an independent term, consisting of year and month, was fitted to the model to account for this trend. In the initial full model, monthly deaths were modeled as a function of laboratory reports for each gastrointestinal pathogen (11 terms), the linear time variable, and a constant term (Table 2). Pathogens were removed if the coefficient was negative (because that was considered not biologically plausible) or if the variable was not significant in the model ($p>0.05$) to give the most parsimonious model. Model coefficients are on the natural scale (i.e., they represent directly how many deaths are associated with each laboratory report). The number of deaths in each month was estimated by multiplying the coefficient from the regression model for the pathogen by the number of monthly laboratory reports for that pathogen. Norovirus activity is highly seasonal; therefore, the number of deaths was also calculated with the year beginning in July and ending in June.

We carried out 2 additional analyses to test whether the 2002–03 season, when a novel norovirus strain emerged, was associated with increased pathogenicity. First, we tested for an interaction between the 2002–03 season and laboratory reports of norovirus. We looked for a significant difference in the relationship between laboratory reports of norovirus and deaths in 2002–03 season compared with other seasons (i.e., effect modification). A higher coefficient would indicate higher pathogenicity in this epidemic

Table 2. Regression model results for deaths from infectious and noninfectious gastrointestinal disease in persons ≥65 years of age, England and Wales, 2001–2006

Pathogen	Initial full model		Final model	
	Coefficient*	p value†	Coefficient*	p value†
Infectious intestinal disease models				
Norovirus	0.0134	0.003	0.0174	<0.001
Astrovirus	–0.059	0.415	–	
Shigella spp.	0.103	0.528	–	
Rotavirus	–0.055	0.003	–	
Campylobacter spp.	–0.017	0.001	–	
Escherichia coli	0.067	0.612	–	
Cryptosporidium spp.	–0.151	0.122	–	
Giardia spp.	–0.165	0.209	–	
Other parasites	–0.012	0.890	–	
Salmonella spp.	–0.011	0.478	–	
Adenovirus	–0.341	0.266	–	
Time trend	1.437	<0.001	1.611	<0.001
Constant	23.11	<0.001	6.239	<0.001
Noninfectious intestinal disease models				
Norovirus	0.0134	0.011	0.0173	<0.001
Astrovirus	0.115	0.198	–	
Shigella spp.	0.240	0.221	–	
Rotavirus	–0.066	0.004	–	
Campylobacter spp.	0.001	0.903	–	
E. coli	–0.088	0.566	–	
Cryptosporidium spp.	–0.125	0.315	–	
Giardia spp.	–0.030	0.860	–	
Other parasites	–0.081	0.439	–	
Salmonella spp.	–0.039	0.050	–	
Adenovirus	0.0147	0.967	–	
Time trend	2.008	<0.001	2.488	<0.001
Constant	20.240	<0.001	11.135	<0.001

*The coefficient represents the number of deaths associated with each laboratory report for each pathogen. The constant (intercept term) indicates monthly deaths associated with other causes.
†Wald test.

season. Secondly, we calculated a ratio of deaths to laboratory reports by dividing the number of deaths with any direct mention of viral gastroenteritis on the death certificate by the number of laboratory reports of norovirus in the corresponding year.

Results

During 2001–2006, a total of 1,136 deaths were recorded with any code for infectious ID and 1,736 for noninfectious ID (Figure 1). Infectious and noninfectious ID–associated deaths were correlated ($R^2 = 0.33$, $p = 0.10$, Figure 1) and exhibited a wintertime seasonal pattern. Over the same period (2001–2006) in England and Wales, a total of 65,932 laboratory reports of the pathogens of interest were submitted for those ≥65 years of age. Summertime seasonality of the major bacterial pathogens and the wintertime seasonality of viral pathogens for this age group are illustrated in Figure 2, panels A–C.

Table 2 shows the comparisons of the best fitting models for infectious and noninfectious ID–associated deaths. Norovirus was the only pathogen significantly associated with monthly counts of infectious ID deaths ($p<0.001$). All other pathogens were removed from the model. In the noninfectious ID deaths model, astrovirus was also significant ($p = 0.02$). Because astrovirus infection is rare in the elderly (*4*) and shares a similar seasonality with norovirus, we decided to leave it out of the final model. A linear term, accounting for the general increasing trend in the number of deaths reported, significantly improved the model ($p<0.001$) and was included in the final estimation. Norovirus remained the only significant pathogen in the model. Therefore, in the final models the expected number of norovirus deaths was modeled as a Poisson distribution of laboratory reports of norovirus and a linear time variable. Some slight overdispersion was evident in the infectious ID deaths model, but fitting an alternative model to account for the overdispersion, negative binomial models, did not substantially alter the results, which suggests that Poisson regression is not inappropriate in this case.

The model estimates that during 2001–2006, a total of 228 deaths from infectious ID were associated with norovirus infection, which represents 20% (13.3%–26.8%) of deaths from infectious ID in those ≥65 years of age; 225 (13% [7.5%–18.5%]) of deaths from noninfectious ID were

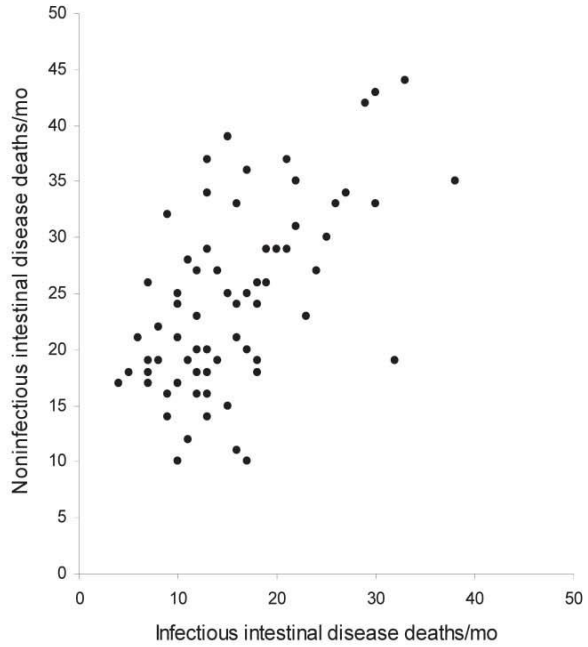

Figure 1. Correlation of monthly death reports of infectious and noninfectious intestinal disease, England and Wales, 2001–2006.

associated with norovirus. Thus, the annual average number of deaths (January to December) from both infectious ID and noninfectious ID was 38; however, when looking at the period from July to June in each year, to account for the norovirus season, the average was ≈40 each season (Table 3). Figure 3, panels A, B, illustrates that models fit better to the deaths from infectious ID but still show some association with the deaths from noninfectious ID.

In years with high seasonal activity, numbers of norovirus-associated deaths were higher. The overall death/laboratory report ratio for 2001–2006 was 55/1,000 (95% confidence interval [CI] 51–60). The ratio did not increase in the years with greater numbers of deaths (Figure 4), and we found no evidence that the ratio was significantly higher during any of the study years. The 2002–03 season had the lowest death/laboratory report ratio. Including an interaction term in the infectious ID model between the epidemic 2002–03 season and laboratory reports of norovirus resulted in a negative-coefficient interaction term (likelihood ratio test p value = 0.002). This finding suggests a lower death/laboratory report ratio in the 2002–03 season, contrary to the hypothesis we were testing. The relative risk for death in the 2002–03 season compared with all other seasons was 0.81 (95% CI 0.69–0.96, p = 0.016).

In an analysis of recorded causes for all infectious ID deaths, viral gastroenteritis was specifically listed as an underlying cause for 13.4% of deaths (152/1,136). Table 4 shows the distribution of recorded underlying causes when viral gastroenteritis was mentioned as a contributory cause in 20% (227/1,136) of infectious ID deaths. For noninfectious ID deaths, diseases of the digestive system accounted for 52% (898/1,736) of the recorded underlying causes. Of these, 92% (829/898) were caused by unspecified noninfectious gastroenteritis and colitis.

Discussion

Over the 6-year period of our study, the total number of deaths in persons ≥65 years of age that may be attributable to norovirus was 453 (228 from infectious ID and 225 from noninfectious ID). On average, this equates to ≈80 deaths each year attributable to norovirus infection. Norovirus was the only gastrointestinal pathogen that was consistently significant in the 2 regression models.

Of the recorded deaths from infectious ID, 13% had viral gastroenteritis listed as the underlying cause. For deaths from noninfectious ID, 48% had an underlying cause of unspecified noninfectious gastroenteritis and colitis. Because these are unspecified causes, and given their similar seasonality with infectious ID, many of these are likely to be infectious causes that were misclassified.

In years with higher norovirus activity, more deaths were associated with norovirus infection. However, we

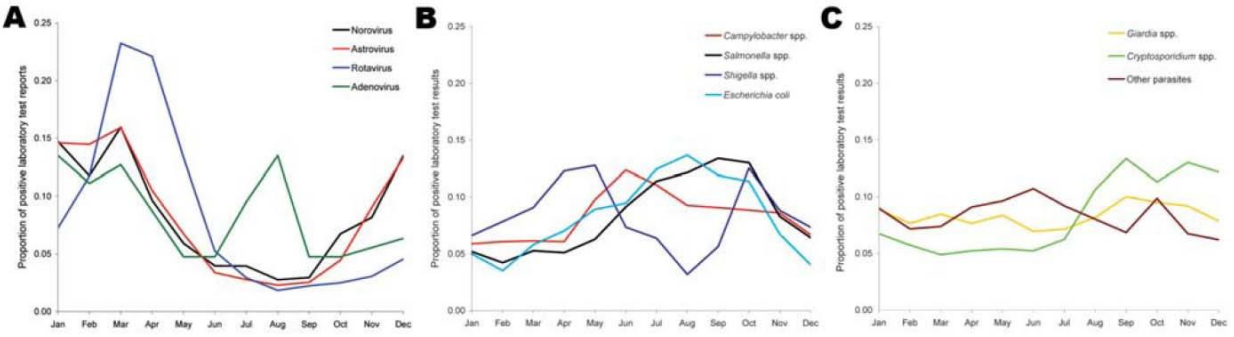

Figure 2. Seasonality of positive laboratory reports of viral (A), bacterial (B), and parasitic (C) pathogens, persons ≥65 years of age, England and Wales, 2001–2006.

Table 3. Estimated number of deaths in each season (July to June) from the regression models, England and Wales, 2001–2006

Year	Predicted annual deaths, no. (95% confidence interval)		
	Infectious intestinal disease only	Noninfectious intestinal disease only	Infectious and noninfectious intestinal disease
2001–02	22.2 (14.7–29.7)	21.9 (12.7–31.2)	44.3 (32.4–56.2)
2002–03	59.5 (39.4–79.5)	58.8 (34.0–83.7)	118.9 (86.9–150.8)
2003–04	18.4(12.2–24.6)	18.2 (10.5–25.9)	36.8 (26.9–46.7)
2004–05	51.4(34.1–68.8)	50.9 (29.4–72.4)	102.8 (75.2–130.5)
2005–06	51.8(34.3–69.3)	51.3 (29.6–72.9)	103.6 (75.7–131.4)
Total	203.3 (134.6–272.0)	201.2 (116.1–286.2)	406.5 (297.2–515.7)
Annual mean	40.7	40.2	81.3

found no evidence of increased pathogenicity in years with higher recorded norovirus activity. The season when a new variant of the genotype II.4 virus emerged (2002–03) did not coincide with an increase in death/laboratory-report ratio. Indeed, the opposite was observed; fewer deaths as a proportion of positive laboratory reports were observed, the interaction term showed a negative coefficient for that season, and the relative risk for death during that season was lower than during other seasons.

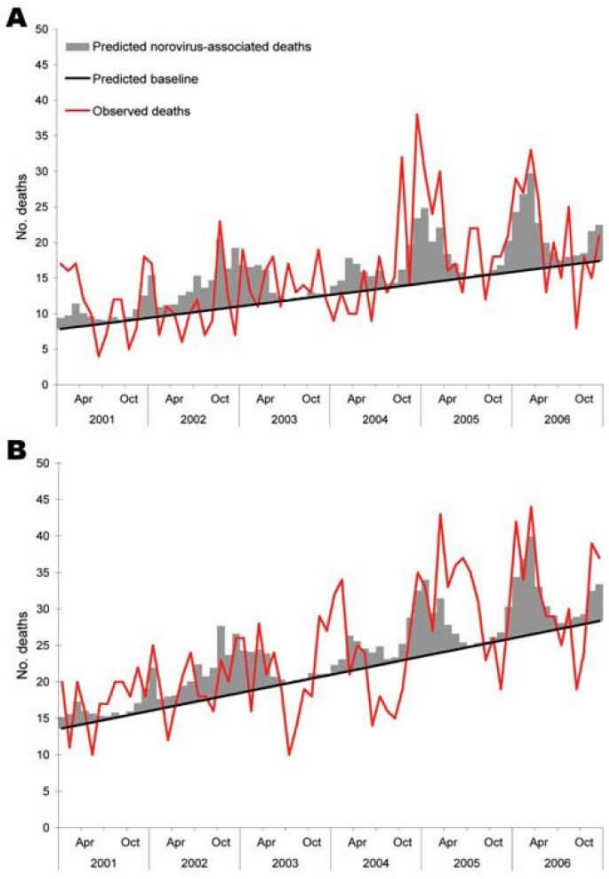

Figure 3. Observed and expected monthly deaths in persons ≥65 years of age from infectious intestinal diseases (A) and noninfectious intestinal diseases (B), derived from the most parsimonious models. England and Wales, 2001–2006.

One of the assumptions in our regression model was that laboratory reporting was consistent over the time of the study. Laboratory reporting processes did not change during the years of the study and are unlikely to have caused bias in this study. Testing and reporting behavior, however, may have changed over time. The number of specimens identified by PCR and ELISA increased from ≈70% to ≈90% in the study period. Thus, the decreased ratio of deaths/laboratory reports may have resulted from increased testing during the 2002–03 season rather than from the virus being less pathogenic during that year.

The modeling approach may underestimate the contribution of norovirus and other pathogens because the method estimates how much of the seasonal variation in death is associated with the seasonal variation in laboratory reports. Less-seasonal pathogens are less likely to show an association, and nonseasonal components (i.e., background levels) will not be attributed to a pathogen. Indeed, a substantial constant term in our models represented these unattributed deaths. The model for deaths from noninfectious ID did not appear to be as good a fit as the model for deaths from infectious ID. There was, in our opinion, enough evidence of a correlation between infectious and noninfectious ID to make a case for including this model.

This method has been used in the past for other pathogens (rotavirus, respiratory syncytial virus, pneumococcus, influenza virus) and unexplained deaths; when we used it in this study, we found an association between norovirus and death. Until our study, most reports of norovirus-associated deaths have been anecdotal (*13*). Although deaths associated with norovirus infection have been documented (*14*,*15*), these are usually singular reports of patients having died subsequent to infection with norovirus, rather than in-depth analysis of time trends of death.

In this study we attempted to go further and estimate the extent of death from norovirus. Norovirus is usually considered a mild, self-limiting disease, and most of those infected with the disease make a full recovery with no long-lasting effects. However, this study shows that part of the population, those ≥65 years of age, have a small risk of dying as a result of contracting norovirus. Rates of infection are higher within healthcare settings than in the commu-

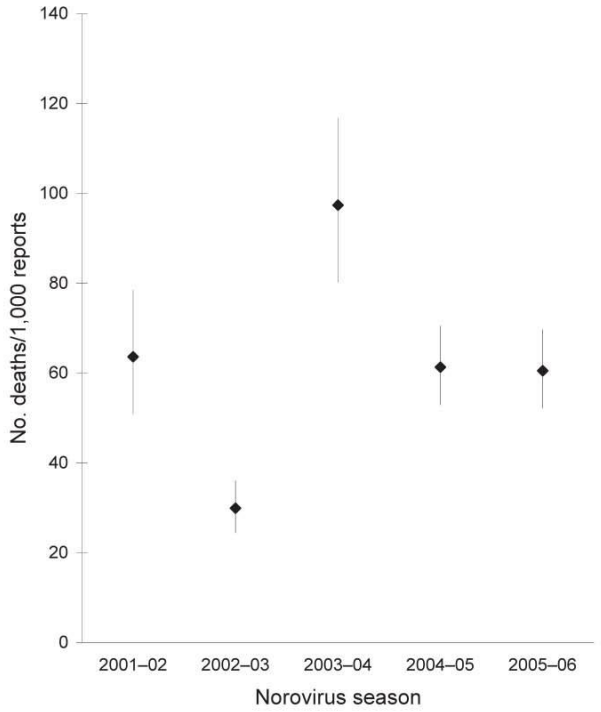

Figure 4. Ratio of viral gastroenteritis–associated death reports to norovirus laboratory reports, 5 norovirus seasons (2001–2006), England and Wales.

nity (*4*,*15*,*16*). Previous studies have shown that hospital patients who are involved in outbreaks of norovirus are ill longer than those who become infected in other settings (*15*). In England the proportion of the population ≥65 years of age is increasing. In years to come, this will be a substantial proportion of persons at risk, and deaths associated with this disease may well increase.

Noroviruses are known to evolve quickly. Emergence of new variants of the most commonly circulating strain can cause epidemic years in which more outbreaks occur and many more persons are infected. New variants are also associated with out-of-season activity, i.e., more outbreaks and infections than usual occurring in summer. When this happens, most of the population may be susceptible to infection. Our study suggests that when such epidemics occur, the number of norovirus-associated deaths increases as a result of the large number of persons infected rather than from increased virulence. Nevertheless, a measurable amount of death is associated with norovirus infection every year.

Table 4. Recorded underlying causes of death in persons in whom viral infectious intestinal disease was a contributory factor

Underlying cause of death	%
Infectious intestinal disease (viral)	40.2
Circulatory system disorder	32.8
Respiratory system disorder	9.0
Neoplasm	4.9
Digestive system disorder	2.5
Nervous system disorder	2.5
Endocrine, nutritional, and metabolic disorders	2.5
Infectious intestinal disease (bacterial)	1.6
Mental/behavioral disorder	1.6
Musculoskeletal and connective tissue disorder	1.6
Genitourinary system disorder	0.8

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Chapter 4. Hospital Admissions Due to Norovirus in Adult and Elderly Patients in England

Hospital Admissions Due to Norovirus in Adult and Elderly Patients in England

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Norovirus generally causes a mild illness in the community. However, modeling routine hospital admission statistics, we estimate that ~3000 norovirus admissions to English hospitals occur per year, accounting for 0.3% and 0.1% of emergency admissions among elderly and adult patients, respectively, at times of peak activity. These admissions pose a risk for subsequent nosocomial infection outbreaks.

Noroviruses are a major cause of sporadic and epidemic gastroenteritis worldwide [1–3]. Although most infections are mild and self limiting [4], some elderly patients or those with preexisting diseases may have more severe illness [5, 6], resulting in hospitalization or even death [7]. Beyond the health impact that results from individual cases, hospital admissions due to norovirus gastroenteritis may seed nosocomial infection outbreaks because the virus is highly transmissible [8]. Norovirus can also be introduced into hospitals by staff and visitors; the relative contribution of introduction and nosocomial transmission to the burden of norovirus infections in hospitals is not known. Outbreaks of norovirus infections in hospitals appear to be increasing [8], with considerable cost implications, because curtailing transmission frequently requires the temporary closure of affected units [9]. We estimate the number of norovirus hospital admissions using an indirect modeling approach because viral testing is only performed on a tiny fraction of cases and norovirus is rarely recorded as a cause of hospital admission [3, 8].

Methods. All admissions to National Health Service (NHS) hospitals in England are recorded in Hospital Episode Statistics (HESonline; http://www.hesonline.nhs.uk), the national statistical data warehouse for England. A single record was extracted for each emergency admission from week 27 of 2000 to week 52 of 2006 in patients 18 years or older with a primary diagnosis of acute infective gastroenteritis (*International Classification of Diseases, 10th Revision [ICD-10],* codes A00–A09, excluding A02.1–9, A05.1, and A06.1–9) or unspecified noninfective gastroenteritis and colitis (code K52.9). Admissions with 1 of these codes in any of the first 3 secondary diagnosis fields were also included if all preceding fields contained codes for typical symptoms of gastroenteritis (eg, abdominal pain, nausea and vomiting, or volume depletion).

LabBase is a national database managed by the Health Protection Agency that contains laboratory reports of pathogens from participating laboratories. Specimens originate from hospitals or primary care physicians. Weekly counts of detections of *Campylobacter, Clostridium difficile, Escherichia coli,* nontyphi salmonellae, shigellae, *Cryptosporidia, Giardia,* astrovirus, norovirus, and rotavirus in feces from individuals 16 years or older in England were obtained.

The number of hospital admissions due to norovirus was estimated by examining the temporal relationship between laboratory reports and hospital admissions. Linear regression models were fitted [10] using Stata statistical software, version 10 (StataCorp), in which variance in the numbers of hospital admissions is explained by variance in the number of laboratory reports. Hospital admissions coded as gastroenteritis without a clearly specified cause (*ICD-10* codes A04.9, A05.9, A07.9, A08.3, A08.4, A09, or K52.9) were modeled as the outcome variable as a function of pathogen-specific counts of laboratory reports. Backward stepwise regression was performed by removing pathogen variables that did not contribute significantly or plausibly to the models ($P > .05$ or negative coefficient). Norovirus diagnostics improved substantially during the study period. The proportion of diagnoses made by relatively insensitive electron microscopy decreased from 88% to 10% from 2001 to 2006, with molecular methods (enzyme-linked immunosorbent assay and reverse-transcriptase polymerase chain reaction) becoming more widely used. To control for these and other unmeasured secular trends, a linear indicator variable for time was included. To estimate weekly norovirus admissions, the norovirus model coefficient was multiplied by the number of laboratory reports. Separate models were fitted for adult (18–64 years) and elderly (≥65 years) patients.

Annual figures for norovirus are provided for the periods of

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1 July to 30 June to reflect the winter seasonality. Denominator data were derived from HES (all emergency admissions) and from the United Kingdom Office for National Statistics (population estimates).

Results. Between July 2000 and the end of 2006, 341,252 emergency admissions of patients 18 years or older to NHS hospitals in England were given diagnosis codes that indicated gastroenteritis with (10.9%) or without (89.1%) a clearly specified infective cause as the main condition. Admissions recorded as K52.9 (77.1%), A04.7 (6.3%), A09 (6.2%), and A08.4 (5.4%) increased markedly in both adult and elderly patients during the study period. The annual *Campylobacter* or *Salmonella* admissions showed no major change. Two hundred ninety-six admissions (0.1%) were specifically coded as due to norovirus. During the study period, 593,424 laboratory reports meeting our criteria were received by LabBase; norovirus accounted for 15,752 of these.

After controlling for other significant pathogens (*Campylobacter,* salmonellae, and rotavirus in the adult model; *Campylobacter* in the elderly model) and time trends, norovirus laboratory reports remained highly associated with hospital admission ($P < .001$ for both; Figure 1). In these models, 8.7% (95% confidence interval [CI], 7.7%–9.8%) and 4.4% (95% CI, 3.0%–5.7%) of cases with an unspecific gastroenteritis code in elderly and adult patients, respectively, were attributed to norovirus infection. In the elderly patients, this proportion exceeded 19% in the 10% of weeks with the highest norovirus activity.

The overall rates of hospital admissions due to norovirus in England were estimated by adding HES records with a code for norovirus infection (accounting for <2% of the total norovirus estimate) to the predicted numbers from the models. Among elderly patients, 799 (95% CI, 707–891) to 3410 (95% CI, 3021–3799) admissions were attributed to norovirus in the seasons with the lowest and highest norovirus activity, respectively, corresponding to 10 (95% CI, 9–11) to 43 (95% CI, 38–48) admissions per 100,000 population. For adults, the corresponding figures were 688 (95% CI, 476–900) to 1485 (95% CI, 1027–1942) admissions and 2.3 (95% CI, 1.6–2.9) to 4.8 (95% CI, 3.3–6.3) admissions per 100,000 population.

Norovirus disease was estimated to cause 1.17 (95% CI, 1.04–1.30) and 0.55 (95% CI, 0.38–0.71) per 1000 emergency admissions in elderly and adults patients, respectively, on average. In the 10% of weeks with the highest norovirus activity, 3 per 1000 emergency admissions of elderly patients and 1.3 per 1000 emergency admissions of adult patients may be due to norovirus.

A range of sensitivity analyses demonstrated that the model results for norovirus were robust. Regression coefficients and CIs were not substantially changed by removing other significant pathogen variables, not controlling for time, or using a Poisson model instead of a linear model. Laboratory reports

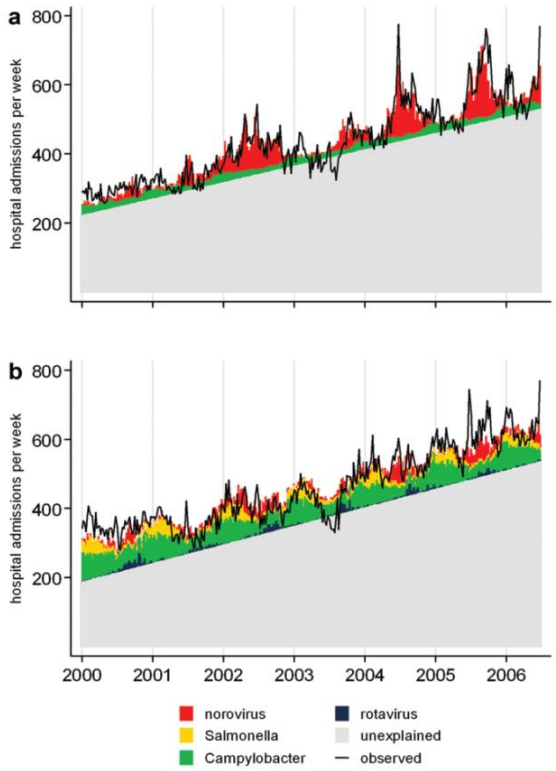

Figure 1. Expected numbers from most parsimonious models and observed counts of weekly emergency admissions associated with unspecified infective or noninfective gastroenteritis. x-axis labels apply to both panels and are positioned at week 27 of each year. *a,* Patients 65 years and older (adjusted $R^2 = 0.89$). *b,* Adult patients younger than 65 years (adjusted $R^2 = 0.85$).

of *C. difficile* increased by >100% during the study period; *C. difficile* was nonsignificant in all models including a time variable. When hospital admissions with pathogen-specific gastroenteritis *ICD-10* codes (other than A08.1, the code for norovirus) were used as outcomes (alone or in combination), norovirus laboratory reports were not significant in any model.

Discussion. We estimate that there are, on average, 2010 and 1050 annual admissions to English NHS hospitals in elderly and adult patients, respectively, because of severe community-acquired norovirus, with >0.3% of all emergency admissions among elderly individuals attributable to norovirus during times of peak activity. The seasonality of hospital admission for nonspecified gastroenteritis in adult and elderly patients follows closely the temporal pattern of norovirus.

Our results are based on administrative data covering virtually all emergency hospital admissions in England and diagnostic data from a large number of laboratories across the country. Our estimates, although indirect, are highly robust to the construction of the statistical model.

The origin of laboratory samples is frequently not recorded; they may stem from patients within institutions (hospitals or nursing homes) and from the community. Samples tested for noroviruses are more likely to originate from outbreaks in semi-closed facilities than from sporadic cases, and the epidemiology of this subset of cases might differ from the rest in terms of timing and amplitude of seasonality. We investigated whether introducing a time lag or lead of up to 2 weeks would improve the correlation, but this was not the case (data not shown). The seasonal pattern of laboratory reports might be affected by reduced testing in summer months, predominantly testing outbreaks, and testing only a few samples from each outbreak. If the explanatory laboratory data were diluted with specimens from a population with different seasonal patterns of disease, the association with hospital admissions would have been weakened, resulting in a conservative estimate. Increasing awareness and availability of diagnostics for norovirus could improve ascertainment of cases and might lead to an increase in the number of reports over the years. We controlled for secular trends in our model, and this did not significantly alter our estimates for norovirus hospital admissions.

In HES, the primary diagnosis is defined as "the main condition treated or investigated during the relevant episode of healthcare." Although in most cases the main condition will be the one that leads to admission, it is conceivable that a nosocomial infection might occupy this place because of either severity or poor coding. We cannot completely rule out this possibility.

Emergency admissions with a nonspecific gastroenteritis code showed a steep upward trend in both age groups throughout the study period. Although *C. difficile* laboratory reports showed a similar increase, their marked seasonal fluctuation (particularly in elderly patients) was reflected in neither the outcome variable of our model nor the number of patients with HES data indicating *C. difficile*–associated disease as the likely cause of admission. This increase in gastroenteritis admissions is not explained by our model and should prompt further scrutiny.

Our estimate of norovirus-associated admissions (~3000 per year) is substantially higher than a previous estimate based on outbreak-associated hospitalizations (~500 per year) [11]. As our analysis demonstrates, norovirus is a common cause of severe gastroenteritis requiring hospitalization. The additional health and economic burden of nosocomial disease from this highly infectious pathogen should also be considered because it may exceed community-acquired disease.

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Potential conflicts of interest. All authors: no conflicts.

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Chapter 5. The development of web-based surveillance provides new insights into the burden of norovirus outbreaks in hospitals in England

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The development of web-based surveillance provides new insights into the burden of norovirus outbreaks in hospitals in England

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SUMMARY

A new surveillance system for outbreaks of norovirus in English hospitals, the hospital norovirus outbreak reporting system (HNORS), was launched in January 2009. On site investigators were enabled to enter data on outbreaks of norovirus directly onto a tailored system via an internet-based front end. A standard dataset was designed to collect information describing the key epidemiological characteristics of each outbreak. In the period 1992–2008, 1817 suspected and confirmed outbreaks of norovirus in English hospitals were reported to national surveillance. After introduction of the new system there were 3980 reports of outbreaks of suspected and confirmed norovirus received in the years 2009–2011. Data from the new reporting system demonstrates that transmission of norovirus levies a heavy burden on English hospitals. On average, reported outbreaks are associated with 13 000 patients and 3400 staff becoming ill, 8900 days of ward closure and the loss of over 15 500 bed-days annually.

Key words: Caliciviruses, Norwalk agent and related viruses, outbreaks, surveillance system.

INTRODUCTION

Norovirus is the commonest cause of outbreaks of infectious intestinal disease (IID) with around 50% of all IID outbreaks attributed to this pathogen [1, 2]. Norovirus outbreaks are most frequently reported in healthcare settings such as nursing homes, other long-term care facilities and hospitals [1, 3, 4]. Nosocomial outbreaks of norovirus impose a heavy cost on institutions. For example, the economic impact of an outbreak in a US hospital in 2004 was estimated to be over US$650 000 [4]; one outbreak in a Swiss hospital cost over US$40 000 [5]; in one health region in Scotland from 2007 to 2009 the estimated excess costs of norovirus outbreaks was around US$1.8 million [6]. The public health and financial impact of norovirus outbreaks in English hospitals was first illustrated by a study conducted in the county of Avon, in South West England, between 2002 and 2003 [7]. Researchers estimated that IID outbreaks (62% of which were due to norovirus) cost the National Health Service (NHS) in Avon US$1.01 million per 1000 beds due to bed-days lost and staff sickness. Extrapolating this to the whole of the NHS in England this equated to approximately US$184 million.

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Following a recommendation of the UK Government's Committee on the Microbiological Safety of Food [8] standardized surveillance of general outbreaks of IID was introduced in 1992 [9]. A review of the surveillance data for the period 1992–2000 on hospital outbreaks of IID provided the first indications of the impact of norovirus infections in hospitals in England [10]. Over a quarter of all general outbreaks of IID reported occurred in hospitals. Almost 80% (1097/1396) of these were confirmed or suspected to be due to norovirus.

It was recognized by the UK Department of Health that more detailed systematically collected information on the epidemiology of norovirus infection in hospitals was required in order to develop a rigorous evidence base to inform national infection control policies. The Hospital Norovirus Outbreak Reporting System (HNORS) was launched in January 2009.

In this paper we present data from the first 3 years of HNORS (2009–2011) in England and contrast it with analyses of data drawn from the national surveillance system for general outbreaks of IID (GSURV) prior to dedicated hospital surveillance (1992–2008). As the previous system (GSURV) is the only benchmark available, this would provide a measure of change, if any occurred, in ascertainment of norovirus outbreaks in hospitals from the introduction of the new system. Routinely gathered laboratory data from positive specimens of norovirus in individuals were used to compare the seasonality of reported outbreaks. Laboratory data from specialist centres (SCs), where samples from outbreaks in hospitals are referred, was used to assess the completeness of the new surveillance scheme (HNORS).

METHODS

Surveillance of general outbreaks of infectious intestinal disease 1992–2008 (GSURV)

Systematic national surveillance of general outbreaks of IID in England and Wales has been in continuous operation since 1992. This system is described elsewhere [10]. Briefly, summary data on outbreaks of IID were reported using standardized paper forms after the outbreak had concluded and were entered onto a database. The items requested on the form included: mode of transmission, place of outbreak, number of cases; number laboratory-confirmed cases; first and last dates of onset of illness. Data for outbreaks of suspected/confirmed norovirus infection in English hospitals from 1992 to 2008 were extracted. Only sparse data on the types of wards affected were available. No data were collected on the numbers of patients *vs.* staff affected in outbreaks, ward closures (number or duration) or bed-days lost.

Hospital outbreak reports 2009–2011 (HNORS)

A standard dataset, with specifications and definitions agreed by consensus, was designed to collect information describing key epidemiological characteristics of each outbreak including: first and last onset dates, number of patients/staff affected, ward/bay closures and bed-days lost. Data were entered onto a secure web-based database (http://www.hpa-bioinformatics.org.uk/noroOBK/) by infection preventionists at NHS hospitals (see Appendix 1 for full list of data items collected). Each NHS Trust† was contacted, via the Director of Infection Prevention and Control (DIPC), to invite them to participate in the reporting system. Each Trust was provided with a log in and password in order to participate. Participation was voluntary.

Definitions

The HNORS reporting system utilizes previously developed definitions of cases and outbreaks [7, 11].

Case definition

A suspected case of norovirus is defined as (*a*) vomiting: $\geqslant 2$ episodes of vomiting of suspected infectious cause occurring in a 24-h period; (*b*) diarrhoea: $\geqslant 2$ loose stools in a 24-h period; or (*c*) diarrhoea and vomiting: $\geqslant 1$ episodes of both symptoms occurring within a 24-h period, where neither criteria (*a*), (*b*) or (*c*) are associated with prescribed drugs or treatments, and are not associated with reaction to anaesthetic or an underlying medical condition or existing illness. A confirmed case of norovirus was defined as: (*a*), (*b*) or (*c*) above with microbiological confirmation.

Norovirus outbreak definition

Suspected outbreak: two or more cases, as defined above, occurring in a ward or bay within the hospital

† NHS Trust refers to the administrative organization for a group of hospitals in the NHS in England and Wales. Some Trusts contain several hospitals within a town or city, while some Trusts contain only one large hospital.

without laboratory confirmation. *Confirmed outbreak*: as above with laboratory confirmation, i.e. with at least one positive specimen.

Reports of both suspected and laboratory-confirmed norovirus outbreaks were requested. Outbreaks of diarrhoea and vomiting can be caused by pathogens other than norovirus. In the absence of laboratory confirmation, the following criteria are provided as guidance to hospitals as indicators of a norovirus outbreak: average duration of illness of 12–60 h; average incubation period of 24–48 h; more than 50% of people with vomiting; no bacterial agent found [12]. Outbreaks are considered to be over if no new cases arise more than 7 days after the last case was reported to be symptom-free.

Laboratory reporting

Two sets of laboratory data were analysed. First, the HPA maintains a well-established laboratory reporting system, described in detail elsewhere, which routinely collects data from laboratories around the UK on positive specimens for many organisms (LabBase2) [9]. These data were used to compare the pattern of norovirus activity, i.e. laboratory reports of individuals who are diagnosed with norovirus [in the period for analysis the majority of whom are tested by polymerase chain reaction (PCR)], with the hospital outbreak reporting system (HNORS). Second, each of the five SCs in HPA regional laboratories and two collaborating centres in London that are routinely sent specimens from patients involved in outbreaks in hospitals, were requested to provide monthly returns on the number of outbreaks for which they had received specimens, with details of the hospital, ward, and dates the outbreaks occurred. The laboratory data from SCs were used to assess the level of ascertainment of outbreaks in hospitals in HNORS using capture–recapture analyses described below.

Estimating the number of unreported outbreaks

Data from SCs were used to estimate the level of under-/overreporting of hospital outbreaks. Hospital-reported outbreaks (HNORS) were matched to those provided by SCs. For details of the matching algorithm, see Appendix 2. The capture–recapture analysis was performed only for regions where there were reports from both systems (six of the nine regions).

Data analysis

We first examined the whole HNORS dataset for all 3 years. The occurrence of norovirus outbreaks peaked during the winter. Therefore, to capture the impact of norovirus over the winter, we designated the beginning of July as the start of a new norovirus season with the end of the following June as its conclusion. We then compared the impacts on hospitals in terms of length of outbreaks, patients/staff affected, ward/bay closures and bed-days lost, which represents an examination of the epidemiology of two consecutive seasons, 2009–2010 and 2010–2011.

Analyses were undertaken using Microsoft Excel 2007 (Microsoft Corporation, USA). All statistical analyses were performed using Stata v. 12 (Stata Corp., USA).

RESULTS

Surveillance of general outbreaks of infectious intestinal disease 1992–2008 (GSURV)

National surveillance (GSURV) received reports of 1485 laboratory-confirmed and 332 suspected outbreaks of norovirus in English hospitals in the period 1992–2008. These outbreaks affected 45 855 people (median 15, range 2–719, IQR 9–24). The duration of outbreaks ranged between 1 and 136 days (median 8, IQR 5–13). Large variations were observed in the annual number of outbreaks reported. Peaks in reporting were observed in 1995/1996 and 2002 (Fig. 1). Outbreak reporting consistently peaked during the winter (Fig. 1).

Hospital outbreak reports 2009–2011 (HNORS)

Between January 2009 and December 2011, HNORS received 3980 reports of outbreaks of suspected and confirmed norovirus from 109 (66%) acute trusts and 41 (51%) community or mental health trusts listed by the NHS Choices website (http://www.nhs.uk/servicedirectories/pages/acutetrustlisting.aspx). Norovirus was laboratory confirmed in 69% (2737) of the reported outbreaks (75% in the 2009–2010 season, 62% in 2010–2011). The outbreaks were reported to have affected a total of 40 007 (median 9, range 0–110, IQR 6–14) patients and 10 620 staff (median 2, range 0–55, IQR 0–4). Outbreaks lasted a total of 24 129 days (median 6, range 1–59, IQR 4–10) and led to 26 717 days of ward/bay closures (median 8, range 1–86, IQR 6–11) and 46 513 bed-days lost (median 12, range 0–288, IQR 6–32). Therefore, on

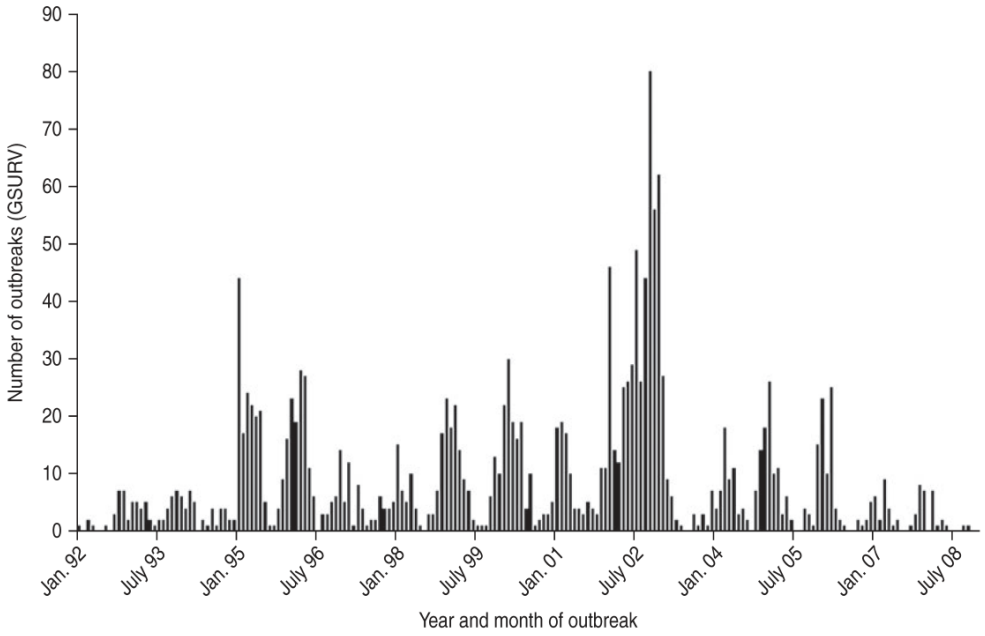


Fig. 1. Outbreaks of confirmed and suspected norovirus in English hospitals by month and year (GSURV), 1992–2008.

average, reported outbreaks are associated with 13 000 patients and 3400 staff becoming ill, 8900 days of ward closure and the loss of over 15 500 bed-days annually. Table 1 shows the number of outbreaks reported by year and by season. In the 2009–2010 and 2010–2011 seasons, 86% and 81% of outbreaks led to ward closures, respectively. The median length of outbreak, length of ward closures and the number of bed-days lost were similar in the two seasons (Table 1). General medicine, care of the elderly, admission wards and trauma and orthopaedics wards accounted for 54% of outbreaks over the 3 years. The median number of patients and staff did not differ between the seasons, although the maximum number of patients affected was higher in season 2009–2010 and the maximum number of staff was higher in 2010–2011.

Seasonal and regional reporting pattern

The majority of outbreaks occurred during the winter months, 78% of all reported outbreaks occurred between October and March, with a particularly high number in the winter of 2009–2010 (Fig. 2). The pattern of reported outbreaks largely follows the pattern of norovirus laboratory reporting in LabBase2. Outbreaks in hospitals were reported from all regions in England. There were slight differences in the reporting pattern in three of the regions (Fig. 3), because not all of them provided data throughout the study period.

Estimating underreporting of outbreaks

SCs reported 1074 and 459 outbreaks in 2009–2010 and 2010–2011 seasons, respectively (Table 2). In the two seasons (2009–2010 and 2010–2011) HNORS reported 3068 suspected and confirmed outbreaks. Using the capture–recapture method, we estimated that over the two seasons the true total of outbreaks of norovirus was 3852, which represents an underreporting of around 20% for the two seasons.

DISCUSSION

The development of a dedicated system, where infection preventionists directly enter data (HNORS), increased reporting of norovirus outbreaks in NHS hospitals in England so that more outbreaks were reported in the system's first full season of operation (2009/2010, $n=1884$) than had been reported in the preceding 17 years ($n=1817$). Data from HNORS demonstrate that norovirus outbreaks levy a heavy burden on English hospitals. Outbreaks are associated with, on average, 13 000 patients and 3400 staff becoming ill each year, 8900 days of ward closure and the loss of over 15 500 bed-days.

Table 1. *Characteristics of reported outbreaks (HNORS)*

Year	Reported outbreaks (*N*)	Patients affected (median, IQR)	Staff affected (median, IQR)	Outbreak duration days (median, IQR)	Days of ward closure (median, IQR)	Bed-days lost (median, IQR)
Year						
2009	851	8972 (10, 6–10)	2370, (3, 1–5)	5868 (7, 4–10)	6296 (8, 6–11)	9805 (10, 5–31)
2010	1775	17864 (9, 6–9)	4592 (2, 0–4)	10340(6, 4–10)	12470(8, 6–11)	21033(11, 6–29)
2011*	1354	13171(9, 5–9)	3298 (2, 0–4)	7921 (6, 4–9)	7951 (8, 6–11)	15675(13, 7–35)
Season						
2009–2010	1884	19476(9, 6–14)	5223 (2, 0–5)	11442(7, 4–10)	13897(8, 6–11)	21954(11, 6–30)
2010–2011	1183	11585(9, 6–14)	3019 (2, 0–4)	7360 (7, 4–9)	7459 (8, 6–11)	15409(14, 7–35)

HNORS, Hospital norovirus outbreak reporting system; IQR, interquartile range.
* Data to 31 December 2011.

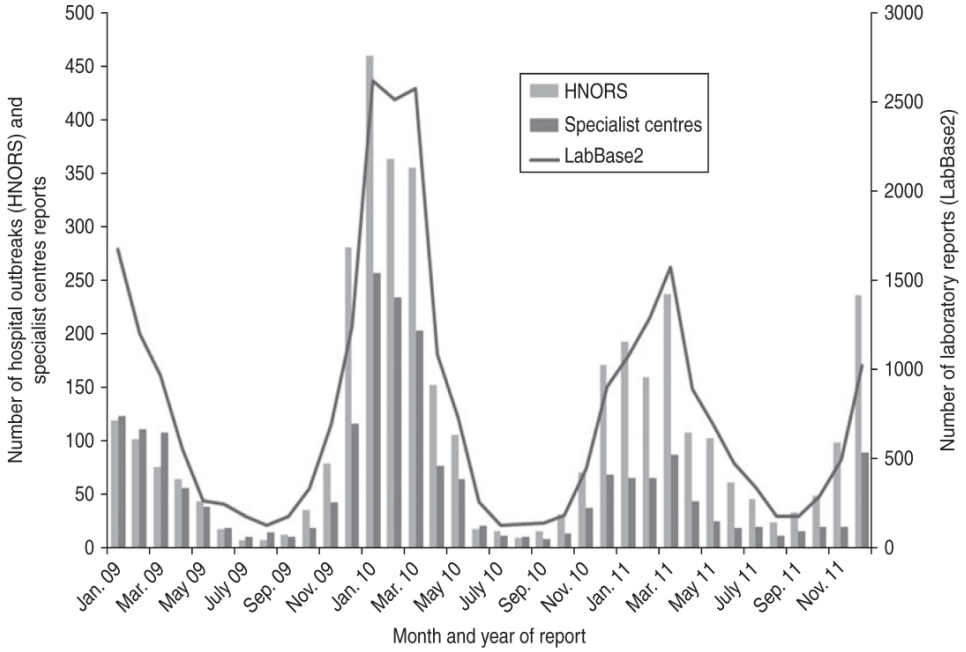


Fig. 2. Number of hospital outbreaks (HNORS) and laboratory reports of norovirus, January 2009 to December 2011.

The first national surveillance system for collecting epidemiological data on general outbreaks of IID in England and Wales was introduced in 1992. Local public health specialists returned epidemiological data on investigated outbreaks using a single 'one size fits all' standardized paper form. This imposed severe limitations on the quantity and types of data that could be collected for each outbreak. The format allowed consistent collection of the following data items for each outbreak: location, setting, pathogen, number affected, hospitalizations, deaths, mode of transmission, vehicle of infection (if foodborne), evidence of association (if foodborne), and contributory factors (if foodborne). Reporting of hospital outbreaks was not routed directly through on-site control of infection teams.

Our analyses show that GSURV provided evidence suggesting that norovirus in hospitals was a matter of major public health concern. In retrospect, this system was able to provide a signal of increases in the number of outbreaks associated with the emergence of new variants of norovirus [13]. However, examination of data from GSURV suggests that reporters varied in their interpretation of what constitutes an outbreak of IID in a hospital. GSURV was limited in that definitions had to be broad enough to apply to a range of settings and modes of transmission captured by the surveillance. For example, defining the spatial

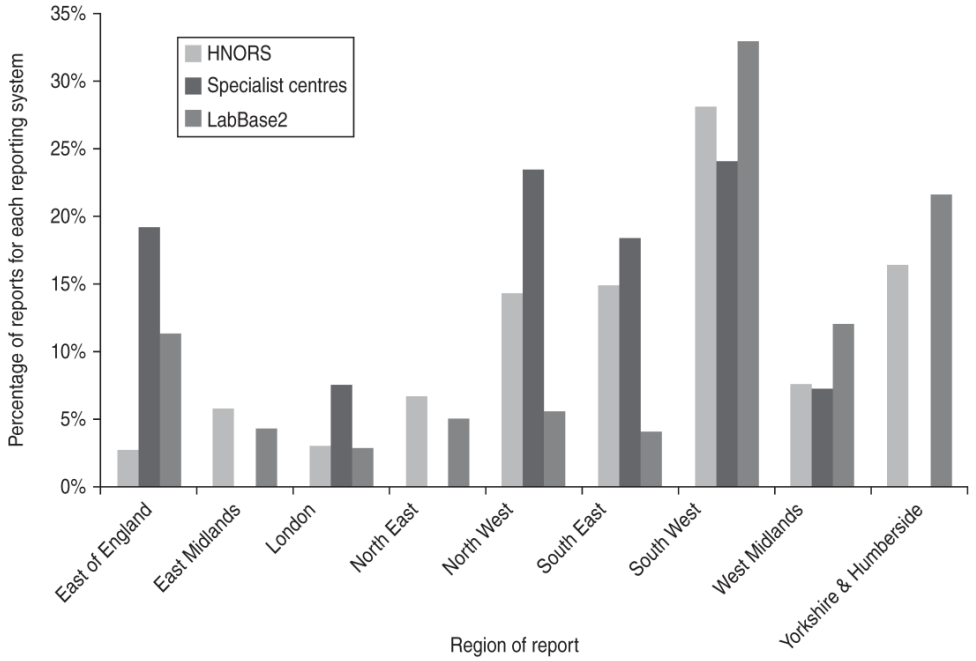


Fig. 3. Percentage of reports received by reporting system in each region, January 2009 to December 2011.

Table 2. *Laboratory-reported outbreaks from specialist centres by HPA region*

HPA region	No. of outbreaks 2009/2010	No. of outbreaks 2010/2011
South East	194	105
London	134	11
South West	206	100
East of England	127	83
East Midlands	33	42
West Midlands	136	19
North East	—	—
North West	236	94
Yorkshire & Humberside	7	6
Total	1073	460

HPA, Health Protection Agency.

boundaries of an outbreak in a restaurant is very different than for in a hospital. In HNORS we were able to provide specific definitions, perhaps the most important being that each hospital unit (or ward) was the area of risk. If an outbreak affected multiple units, we asked for separate outbreak reports and used strict definitions based on the Avon study [7]. Thus while we have inferred that ascertainment of outbreaks has increased following the introduction of HNORS we cannot be sure of the extent of the improvement. Reporters to HNORS are given guidance on case definitions which means that we can be assured that the outbreaks within the database conform to a stricter epidemiological standard. Conversely, the GSURV dataset on hospital outbreaks contains data on a variety of types of events. Given the numbers affected in outbreaks in the GSURV dataset it is likely that the hospital outbreak count in GSURV would be higher because outbreaks affecting more than one ward are commonly reported as a single outbreak in GSURV. This would not have happened if reporters had been given the same guidance as reporters to HNORS.

The HNORS development working group decided that it was important to collect data on the types of wards/units affected in outbreaks. Care of the elderly wards account for 16% of reported outbreaks, the early evidence collected indicates that the spread of norovirus is not narrowly confined to particular ward types.

The planning process to design a new surveillance system for the collection epidemiological data on outbreaks of norovirus in hospitals began in 2008. By this time the use of the internet for surveillance was well established [4, 14]. As a consequence it had become possible to design more sophisticated and flexible data collection instruments. Therefore by working with data providers on the design of the surveillance

system it was possible to focus on specific data items that outbreak investigators could gain ready access to and which were of epidemiological value. It was recognized that, even using a voluntary system, transferring the responsibility for reporting directly to on-site staff was likely to lead to improvements in both the reliability of the data collected and ascertainment. The benefits of empowering stakeholders by providing access to the national database while preserving hospital confidentiality were recognized at an early stage. The most important benefits gained from the adoption of HNORS stem from: (*a*) the use of clear user-drawn case definitions, (*b*) the collection of impact measures, and (*c*) real-time contributor access to the national database and its data analysis tools.

It should be borne in mind that HNORS is a voluntary reporting system and complete ascertainment of outbreaks could not be expected. Our capture–recapture analysis suggests that although ascertainment fell during its second season of operation, reporting of laboratory-confirmed outbreaks remained above 60%. The comparison with routine laboratory reporting (LabBase2) showed that outbreak reporting was sensitive to increased norovirus activity, i.e. it followed the norovirus seasonality exhibited by laboratory reporting. Furthermore, the number of outbreaks reported in the winter of 2009/2010 was greater than the following season when laboratory reports were also greatly increased compared to previous and subsequent years.

There are limitations to the capture–recapture approach [15]. The assumption that capture from one system (HNORS) is unrelated to the likelihood of capture of outbreaks in the other system (data from SCs) might have been violated. We also used only outbreaks from HNORS that were laboratory confirmed but this did not alter the results substantially (data not shown). HNORS is likely to underestimate the number of outbreaks that are laboratory confirmed especially if laboratory confirmation occurs after the outbreak is reported and this information is not updated. Data from the SCs did not have such rigorous definitions of an outbreak, in which case this could have overestimated the number of outbreaks reported from the SCs. This might have overestimated the level of underreporting especially if reports from SCs were not outbreaks but were data from sporadic cases and therefore would not match outbreaks reported to HNORS. Despite these limitations, and in the absence of any other data source available, the estimates from the capture–recapture method are likely to provide a good indication of under-ascertainment. The geographical distribution of outbreaks and laboratory reports (Fig. 3) suggests that there are geographical variations in the application of virological investigations of outbreaks of IID in hospitals. As such our calculations are conservative and might still underestimate the impact of norovirus outbreaks in English hospitals.

One of the features of norovirus outbreaks that make it distinct from some other hospital-acquired infections is the effect it has on staff. Staff illness accounted for 20% (10260/50267) of cases in outbreaks over 3 years. After accounting for underreporting we estimate that this equates to 5000–6500 cases of staff illness in hospitals in England each year. Assuming an average of 4 days absence from work per illness episode this would result in 20000–25000 staff days lost per year. Norovirus outbreaks are most frequent in winter [16] (Fig. 2) which is when hospitals are most busy [17]. Thus the pressure resulting from norovirus staff illness might be greater than the raw data suggests.

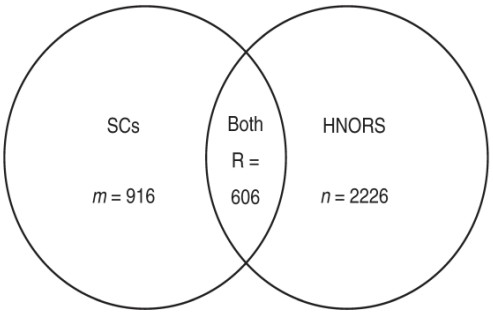
The recently published Second Study of Infectious Intestinal Disease in the Community shows that norovirus is the most common cause of IID in the UK [18]. The application of multiplex PCR tests was successful in increasing diagnoses of norovirus infection in specimens taken by general medical practitioners. The strains identified in outbreaks in community settings appear to be more diverse than those affecting healthcare settings, where the latter are dominated by noroviruses of genogroup II.4 [19]. Understanding more about the interrelationship between community- and hospital-acquired norovirus might assist in the control of infection in hospitals. To make this possible it will be necessary to develop robust sampling frames to collect specimens from patients at primary care and in hospitals for virological analysis through genome sequencing.

In summary, data from HNORS has provided a more complete picture of the major public health problem resulting from norovirus outbreaks in NHS hospitals in England. Such outbreaks are frequently reported from hospitals from nearly all highly industrialized countries. However, the magnitude of the problem that we describe in English hospitals has not been reported elsewhere. Whether that is a result of a smaller burden or just underreporting in other settings can only be known when robust surveillance systems similar to HNORS are implemented in other countries.

APPENDIX 1. *Data fields for HNORS reporting form*

Region*	Ward/bay closed to admissions
Organization*	If yes:
Reporter name*	Date ward/bay closed
Reporter email	Date ward/bay opened
Hospital ward name*	Number of bed-days lost
Ward type	Has the outbreak been confirmed in the laboratory?
Number of beds on ward/bay	Number of specimens
Number of patients affected	Number of positive specimens
Number of staff affected	Laboratory reference number
First date of onset*	Is the outbreak ongoing?
Last date of onset	Comments

* Compulsory field.



N = n^*m/R
N = 3365
Underreporting fraction = $(N-n+R)/(n+R)$
Underreporting fraction = 0·19 (19%)

Fig. A1. Venn diagram illustrating capture–recapture and calculation of underreporting.

APPENDIX 2. Matching method

Estimated ratio of non-reported outbreaks to reported outbreaks is estimated based on capture–recapture methods to calculate the total number of outbreaks. The total number of outbreaks was calculated as $N = n^*m/R$, where n is the number of HNORS-only reported outbreaks, m is the number of laboratory-only reported outbreaks, and R is the number of outbreaks in both web and laboratory systems (Fig. A1).

Outbreaks are considered to be a match (R) if they (*a*) occurred in the same Trust and hospital, and (*b*) where the first date of onset of illness in the reported outbreak and the specimen dates were within 14 days of each other, and (*c*) did not have different ward names. The ward name is often missing from the laboratory data; therefore, if criteria (*a*) and (*b*) were met and ward name was missing from the laboratory data, the outbreaks were still considered a match. This gives a large estimate for R, and therefore a conservative (low) estimate of the total number of outbreaks (N). The reporting ratio was then calculated as: $(N-n+R)/(n+R)$.

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DECLARATION OF INTEREST

None.

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Chapter 6. Infection control measures for norovirus: a systematic review of outbreaks in semi-enclosed settings

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REVIEW

Infection control measures for norovirus: a systematic review of outbreaks in semi-enclosed settings

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KEYWORDS
Gastrointestinal disease;
Gastrointestinal infection;
Hospital;
Infection control;
Norovirus;
Outbreaks

Summary We carried out a review of published, peer-reviewed articles to assess the evidence for effectiveness of control measures during norovirus outbreaks in enclosed settings. There were 47 papers identified for review, some of which reported more than one outbreak, providing 72 outbreaks for analysis. We extracted the following data items: attack rates; the number of people affected and at risk, case or outbreak definition; whether outbreak control measures were implemented; and claims of effectiveness of interventions. We analysed the data to identify any differences in the outbreaks experienced in different settings and any differences experienced during outbreaks according to whether control measures were implemented or not. All of the reviewed papers described outbreaks occurring in industrialised countries. We found no evidence that implementing infection control measures affected the duration of outbreaks, or the attack rates either overall (all settings combined) or within particular settings. The median outbreak duration was 16 days (range: 1–44) compared with 14 (range: 2–92) where control measures were and were not utilized, respectively. Sound infection control procedures are key to controlling norovirus outbreaks but unfortunately, the present body of the published literature does not provide an evidence-base for the value of specific measures.

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Introduction

In temperate climates norovirus infections are highly seasonal, peaking during the winter, and this seasonality is especially marked in healthcare settings.[1–5] Norovirus outbreaks in hospitals cause considerable disruption at times when there is already increased pressure on beds. In a prospective study of outbreaks of gastrointestinal illness in hospitals and nursing homes the cost to the National Health Service in England was around £115 million in one year, making it one of the most costly nosocomial infections alongside urinary tract infections (around £124 million).[6,7] In the same study, gastrointestinal outbreaks in hospitals were longer if affected wards were not closed to new admissions within three days of outbreak onset.[6]

Norovirus gastroenteritis in hospital patients tends to last longer than episodes in nursing home residents or otherwise healthy adults, with 10% of patients still ill after seven days.[8] There is also substantial mortality in infirm elderly groups.[9] Patients with chronic underlying conditions can become severely ill.[10] People in hospital may be more vulnerable due to pre-existing conditions, which can be exacerbated by acute gastroenteritis.

In England, guidelines for managing hospital outbreaks of norovirus were published in 2000.[11] Control measures include paying particular attention to hand washing before and after contact with ill patients, affected staff remaining off work until 48 h after their symptoms have resolved, cohort nursing ill patients, and restricting staff movements between affected and unaffected areas.

We carried out a review of published, peer-reviewed articles to assess the evidence for effectiveness of control measures during norovirus outbreaks in terms of their impact on outbreak size, duration and attack rate.

Methods

Criteria for inclusion

Papers were eligible for inclusion in this review if they were reports of outbreaks of norovirus infection occurring in enclosed or semi-enclosed settings, such as hospitals, nursing homes or cruise ships. Reports had to include attack rates, or enough information on numbers at risk, and affected, so that attack rates could be calculated. Outbreaks reported as foodborne or waterborne in origin were included if they occurred in an enclosed setting and were then associated with secondary spread. Foodborne outbreaks in restaurants were excluded.

Search strategy

We adopted a two-stage strategy. First, to identify all articles published in the English Language on norovirus we used the following keyword search terms in the title and abstracts of published work: norovirus, small round structured virus, Norwalk virus, SRSV, small round virus, Norwalk-like virus, winter vomiting disease, and gastric flu; in the first instance to capture all publications of interest. We performed searches on the following databases: PubMed, Medline, Google Scholar, and Embase for articles published in English or with English abstracts up to July 2008.

Second, to refine our search to concentrate on enclosed and semi-enclosed settings and control measures we performed a second search of the abstracts and titles identified in stage 1 for the terms: hospital, outbreak, outbreak control, control measure(s), semi-closed environment, semi-enclosed environment, nursing home, cruise ship, school. J.P.H. read the abstracts of all the papers selected from this search to identify reports of outbreaks of norovirus. This included all papers on outbreaks reported in enclosed or semi-enclosed settings and where data may be pooled for meta-analysis.

We extracted the following data items: attack rates; the number of people affected and at risk, case or outbreak definition; whether outbreak control measures were implemented; and claims of effectiveness of interventions. We analysed the data to identify any differences in the outbreaks experienced in different settings and any differences experienced during outbreaks according to whether control measures were implemented or not. We reviewed the reference lists of the reviewed papers to identify any published studies not identified in the database literature search.

Meta-analysis

In meta-analyses, treatment effect estimates obtained from combining data from multiple studies are precise but may be misleading due to biases in the studies.[12] This is particularly true of data obtained from observational studies, as reported here.[12] A test for study heterogeneity was performed and was highly significant; therefore providing pooled estimates was inappropriate. We compared the length of outbreak, attack rates and number of people affected by setting and

carried out comparisons of these measures in outbreaks where infection control measures were implemented compared with those where they were not implemented. Comparisons were carried out using the Mann–Whitney rank sum test.

Results

The first search of titles and abstracts returned a total of 1983 papers. The second search reduced this to 125 papers of possible interest. Scanning the abstracts of these 125 papers identified 47 papers for inclusion in the final analysis. In this review, papers reporting more than one outbreak, or separate data for outbreaks in multiple institutions, are included as separate outbreaks. Multiple outbreaks were reported in seven papers—either outbreaks linked to more than one area in one institution or linked outbreaks occurring in more than one institution, giving 23 outbreaks for analysis.[13–19] Two separate attack rates were reported in one paper from two cohort studies of visitors to a health club.[20] For this review the data were treated as two separate outbreaks. In one paper six outbreaks were reported.[14] A single strain of norovirus was detected in all the outbreaks, so the authors argued that it was probably one protracted outbreak affecting several institutions; however, there was no clear evidence of social interactions between institutions that could explain the spread from one to another. This provided a total of 72 reported outbreaks for analysis.

Country and setting of outbreaks

Table I shows the country and setting of outbreaks in the papers we reviewed. All of the reviewed papers were of outbreaks occurring in industrialised countries. Twenty reports (42%) were from the USA, 15 from Europe, 7 (47%) of which were of outbreaks in the UK. One outbreak occurred on a cruise ship travelling from the UK to the USA, and so for the purpose of this review we included it in outbreaks reported from the UK.[21]

The majority of papers related to outbreaks in hospitals and nursing homes. Three papers concerned outbreaks in mixed hospital and nursing home settings[13,22,23] and one paper reported an outbreak affecting a nursing home and two other health care institutions.[24] Other settings were ships,[19,21,25] camp sites,[16,26] health clinics (health

Table I Outbreaks reported by country and setting

Country	Setting	Reference
Australia	Hospital and nursing homes	23
	Nursing home	32,17
Austria	Hospital and nursing home	22
Canada	Hospital	33,34
	Mixed hospital/nursing home	35
China (Hong Kong)	Hospital	36
Finland	Rehabilitation centre	20
Germany	Hospital	10
	Health clinic	27
Israel	Nursing home	14
Japan	Multiple health institutions	24
	Nursery	29
	Hospital and nursing home	13
Netherlands	Nursing home	37
New Zealand	Hospital	15
Spain	Hospital (long-term care facility)	38
Switzerland	Hospital	39,40
UK	Hospital	41–45
	Restaurant	31
	Ship	21
USA	Nursing home	46–53
	Hospital	18,54–58
	Ship	25,19
	Camp site	26,16
	School	28
	Daycare centre	30

spas),[20,27] schools/nurseries[28–30] and one in a restaurant.[31] We included the restaurant outbreak because it was shown to be due to person-to-person spread rather than foodborne in origin.

Attack rates

Outbreaks occurring in ships affected a significantly higher number of people (median: 237; range: 118–432) compared with other settings (rank sum test, $z = -4.239$; $P < 0.0001$). The highest median attack rates occurred in healthcare settings, nursing homes and hospitals (median: 50 and 44 respectively) but this was not significantly higher than in other settings (rank sum test, $z = -1.637$; $P = 0.1017$). The median attack rate in staff or crew was lower than that for patients or passengers. There were no data reported on staff members in the outbreaks occurring in the campsites, restaurant or the health club.

Figure 1 illustrates the variation in published attack rates in hospital and nursing home outbreaks. Attack rates in patients were similar in hospitals and nursing homes. In nine (43%) of the hospital outbreaks and 13 (48%) of the nursing home outbreaks the attack rates were $\geq$50%. The median number of affected patients was higher in nursing home outbreaks (56; range: 8–155) compared with hospitals (30; range: 3–95) (rank sum test, $z = 2.383$; $P = 0.0172$). There was no significant difference in the attack rates in staff or the number of staff affected in outbreaks in hospitals compared with outbreaks in nursing homes (data not shown).

Duration of outbreaks

Outbreaks were longest in healthcare settings; with the median length of outbreaks in hospitals lasting 19 days (range: 6–92) and nursing homes 16 days (range: 3–44), there was no significant difference between the length of outbreaks in hospitals compared to nursing homes (rank sum test, $z = 0.634$; $P = 0.5$). In non-healthcare settings outbreaks were significantly shorter, the median length of outbreak being 7 days (range: 1–26) (rank sum test, $z = -4.024$; $P = 0.0001$).

Infection control measures

The application of infection control measures was identified in 29 papers (47 outbreaks). Table II summarises the data on length of outbreak and attack rates by setting, comparing outbreaks where papers reported implementing infection control measures with outbreaks where no infection control measures were apparently implemented. Implementing infection control measures did not appear to affect the duration of outbreaks, nor the attack rates overall (all settings combined) or within settings. The median outbreak duration was 16 days (range: 1–44) compared with 14 days (range: 2–92).

The median day on which infection control measures were implemented was 5 (range: 1–38). Where attention to hand hygiene was emphasised it was not clear if this meant using soap and water, or using alcohol-based hand wash instead. Four papers explicitly mentioned the use of hand gels.[15,20,38,45]

Environmental cleaning as an important control measure was identified in 16 papers, only two of which did not occur in healthcare settings. All 16 mentioned use of a dilute hypochlorite (bleach) solution. The description of environmental controls in outbreaks on board ship was limited to describing the sanitary inspection and emphasised safe sewage disposal and inspecting food preparation. Thorough environmental cleaning between cruises was discussed in one paper.[21]

In 24 papers restrictions for infected staff were mentioned, and all included the statement that infected staff should be excluded until 48 h after cessation of symptoms. Some authors discussed the feasibility of exclusion during outbreaks since there is often pressure for staff who have been ill to return to work early. In the paper discussing the outbreak at a camp site ill people were effectively quarantined by preventing them from taking part in activities that could cause spread of the infection until 48 h after the symptoms had resolved.[26]

It was claimed that implementing control measures shortened the outbreaks in ten of the published papers.[15,20,23,24,36,38,42–44,54] We found no evidence of shorter duration of outbreaks or lower attack rates in outbreaks where control measures were outlined (Table II).

Discussion

Our aim was to identify norovirus outbreaks in enclosed and semi-enclosed settings and to attempt to elucidate the effect of infection control measures in shortening or reducing the impact of such outbreaks. This review included 72 outbreaks of norovirus in enclosed or semi-enclosed settings from 47 papers. Most occurred in the healthcare settings and all of the reports were from developed countries. We found that outbreaks on cruise ships affected higher numbers of people but outbreaks in the healthcare

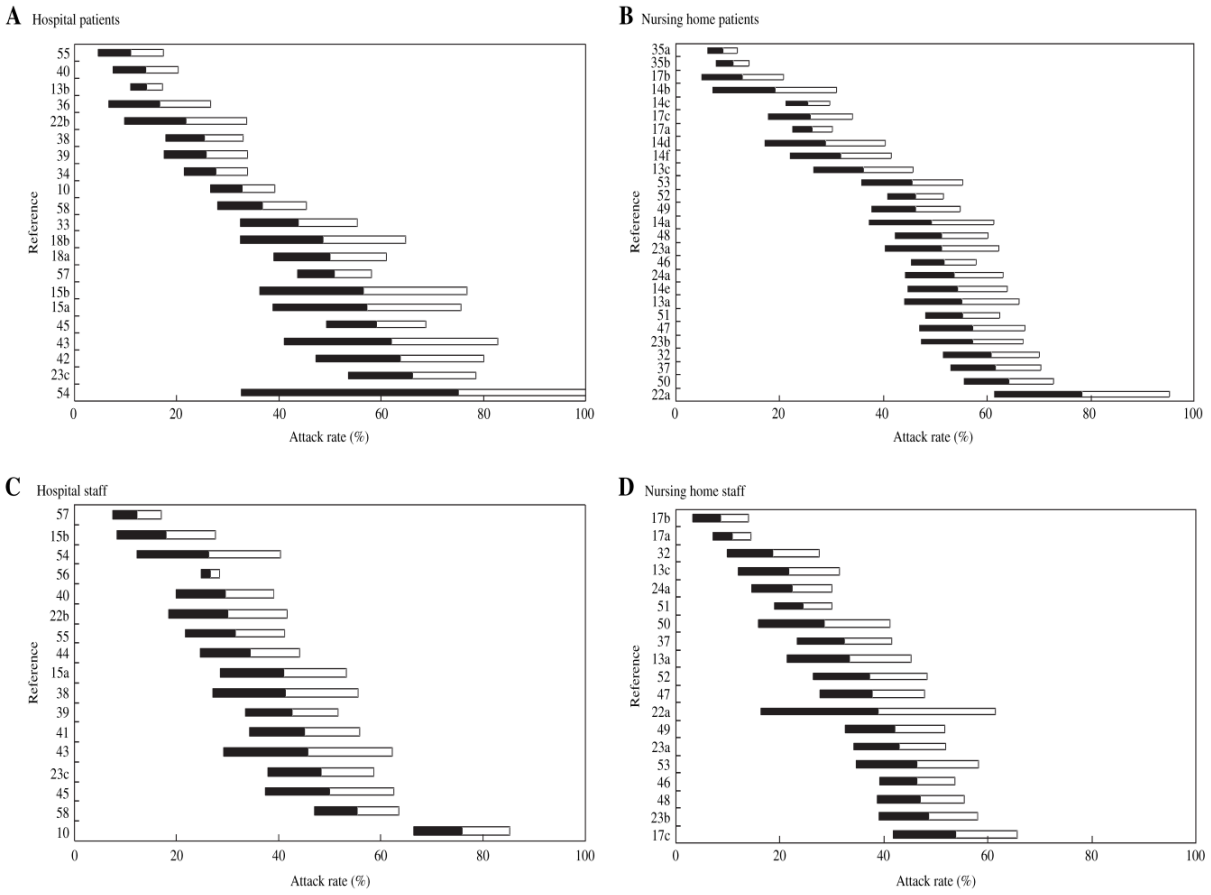

Figure 1 Attack rates (and 95% confidence intervals) in patients and staff during norovirus outbreaks in hospitals and nursing homes. (A) Hospital patients, (B) nursing home patients, (C) hospital staff, (D) nursing home staff.

Table II Comparison of outbreaks by use or non-use of infection control measures

Comparison measure	Infection control measures[a]		Mann–Whitney rank sum test
	Used	Not used	
Length of outbreak (days)			
All settings	16 (1–44) [47]	14 (2–92) [24]	$z = -0.432$ $P = 0.6657$
Healthcare	18 (3–44) [39]	22 (9–92) [11]	$z = 0.751$ $P = 0.4527$
Hospital	17 (6–37) [17]	25 (9–92) [6]	$z = 1.649$ $P = 0.0991$
Nursing home	20 (3–44) [22]	14 (14–26) [5]	$z = -0.407$ $P = 0.6842$
Other	6.5 (1–16) [8]	10 (2–26) [13]	$z = 1.197$ $P = 0.2312$
Attack rate (%) (patients/customers)			
All settings	47.6 (4.3–78.3) [46]	36.1 (11.0–62.6) [23]	$z = -1.044$ $P = 0.2966$
Healthcare	49.6 (9.0–78.3) [38]	41.1 (11.0–55.1) [10]	$z = 1.117$ $P = 0.264$
Hospital	49.5 (13.9–75.0) [16]	32.9 (11.0–51.0) [5]	$z = -1.486$ $P = 0.1372$
Nursing home	50.2 (9.0–78.3) [22]	46.1 (36.1–55.1) [5]	$z = -0.125$ $P = 0.9006$
Other	29.2 (4.3–60.1) [8]	31.1 (16.7–62.7) [13]	$z = 0.507$ $P = 0.6122$
Attack rate (%) (staff/crew)			
All settings	34.4 (0.0–66.1) [29]	32.4 (6.9–100) [16]	$z = 0.261$ $P = 0.7942$
Healthcare	34.4 (0.0–66.1) [27]	37.3 (12.0–75.9) [11]	$z = 0.789$ $P = 0.4304$
Hospital	34.4 (0.0–66.1) [13]	38.3 (12.0–75.9) [6]	$z = 0.439$ $P = 0.6610$
Nursing home	35.1 (6.0–53.7) [14]	37.3 (21.7–47.1) [5]	$z = 0.463$ $P = 0.6463$
Other	22.1 (3.4–40.7) [2]	23.4 (6.9–100) [5]	$z = 0.387$ $P = 0.6985$

[a] Values are median (range) [*N*].

setting were significantly longer. The median number of affected patients was higher in nursing home outbreaks than in hospitals. We detected no significant differences in these parameters between outbreaks where infection control measures were implemented and outbreaks where they were not. We found only one paper where the evidence for shorter duration of outbreak when infection control measures were implemented early was robust.[6] However, this does not mean that we advocate abandoning infection control measures in outbreaks of norovirus in healthcare and other enclosed or semi-enclosed settings, but rather that, in the main, the quality of the papers that we reviewed militated against a firm conclusion either way.

The literature search was limited, since we confined our search to articles published in the English language and the bulk of the review work was carried out by one author only (J.P.H). We focused on major databases such as PubMed and Medline, and attempted to identify further studies by searching Google Scholar and Embase. Despite using very strict inclusion criteria, we identified a substantial number of papers.

Lack of description of control measures does not necessarily mean that they were not implemented, merely not discussed. However, for the purposes of this review we assumed that where control measures were not discussed they had not been implemented. This will almost certainly have led to some studies being wrongly classified as having no infection control methods implemented during an outbreak. Furthermore, if control measures were employed late in an outbreak, and onward transmission is already well established, so the measures would have limited effect.

Although many of the papers that we reviewed included discussion of infection control measures, and some authors claimed that the instigation of these measures stopped or shortened the outbreak, we found no clear evidence in the form of post-intervention evaluations to substantiate these claims. Moreover, where specific interventions, such as hand washing, were mentioned authors often failed to describe specific methods, i.e. whether they advocated soap and water or the use of alcohol hand gels.

There were also shortcomings in the papers that we reviewed. For example, few authors identified the index case in outbreaks. Some showed evidence for the epidemic curve of infections beginning with infected staff and then spreading to patients[24,34,46,48,51] and vice versa in others.[22,40,41,53] Some investigators showed clear associations between the amount of staff contact with patients and risk of illness[23,32,37,38,41,44,47,50,51,53] and in some an increased risk of spreading the disease between patients was demonstrated.[32,47] Reporting of studies in accord with the ORION (Outbreak Reports and Intervention studies Of Nosocomial infection) statement will be beneficial to future comparisons of reports of nosocomial outbreaks of norovirus.[59]

The finding that outbreaks were longer in healthcare settings compared to other settings is perhaps not surprising. Outbreaks in other settings are self-censoring, e.g. people attending a cruise or camp site for a holiday will do so for a short finite time. One group will leave; cleaning can take place before the next group joins. There is no such luxury in outbreaks in hospitals. The case mix tends to be varied and in most wards where people stay for only a short time; there is a constant turnover of new susceptible people coming and going during the outbreak. Second, in non-healthcare situations, the population are healthier and recognising an outbreak tends to be easier. Patients in hospitals or long-term care facilities may have diarrhoeal illness for other reasons, e.g. drugs administered for their care, or pre-existing medical conditions, so an outbreak might not be recognised for some time.

In the guidelines on managing outbreaks of norovirus in hospitals by Chadwick *et al*. only one of the recommended control measures, hand washing, was based on evidence strongly supported by experimental epidemiological studies.[11] The others were based either on recommendations from experts in the field which were based on strong rationale and suggestive evidence, or on recommendations where there was no consensus on the evidence.[11] There are four recent reviews related to infection control on the Cochrane database,[60–63] only one of which contains definitive results showing that hand washing decreased diarrhoeal episodes by 30%.[61]

In a recently published review of reported enteric outbreaks in long-term care facilities, not restricted to norovirus, the authors attempted to identify recommendations to prevent the spread of infection, but in none of the published reports included in their review were the suggested recommendations evaluated with sufficient rigour.[64]

It is difficult to assess which infection control measures are the best at breaking the chain of infection. One crucial factor in determining the best control methods is a better understanding of how infections spread through an institution.[29] Documenting the chain of transmission, from one person to another, linked to molecular epidemiology can assist. In a recent study, examining the hypervariable region of the virus was found to be a more useful predictive tool in linking outbreaks compared with simple genotype analysis.[65] The challenge then is to undertake systematic and rigorous data collection during a series of outbreaks in hospital settings and tie in with the molecular analysis and gain a better knowledge of how outbreaks spread. Analysis detailing the proximity of those affected after the index case has been identified may lead to an understanding of the relative importance of the different methods of transmission and where best to target infection control efforts.

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Chapter 7. Does spatial proximity drive norovirus transmission during outbreaks in hospitals?

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Does spatial proximity drive norovirus transmission during outbreaks in hospitals?

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ABSTRACT

Objective: To assess the role of spatial proximity, defined as patients sharing bays, in the spread of norovirus during outbreaks in hospitals.

Design: Enhanced surveillance of norovirus outbreaks between November 2009 and November 2011.

Methods: Data were gathered during 149 outbreaks of norovirus in hospital wards from five hospitals in two major cities in England serving a population of two million. We used the time between the first two cases of each outbreak to estimate the serial interval for norovirus in this setting. This distribution and dates of illness onset were used to calculate epidemic trees for each outbreak. We then used a permutation test to assess whether proximity, for all outbreaks, was more extreme than would be expected by chance under the null hypothesis that proximity was not associated with transmission risk.

Results: 65 outbreaks contained complete data on both onset dates and ward position. We estimated the serial interval to be 1.86 days (95% CI 1.6 to 2.2 days), and with this value found strong evidence to reject the null hypothesis that proximity was not significant ($p<0.001$). Sensitivity analysis using different values of the serial interval showed that there was evidence to reject the null hypothesis provided the assumed serial interval was less than 2.5 days.

Conclusions: Our results provide evidence that patients occupying the same bay as patients with symptomatic norovirus infection are at an increased risk of becoming infected by these patients compared with patients elsewhere in the same ward.

ARTICLE SUMMARY

Article focus

- Published literature on norovirus outbreaks does not provide clear evidence of the effectiveness of infection control measures.
- Improved understanding of how norovirus spreads in closed environments could lead to better infection control procedures.
- This study uses statistical modelling methods to assess whether patients in proximity are at increased risk of contracting norovirus during outbreaks in hospitals.

Key messages

- We have shown a clear role of spatial proximity in the transmission of norovirus in hospital outbreaks.
- Patients who are in the same bay as patients who become ill have a higher probability of becoming ill compared with patients in a different bay.
- Increasing barriers to movement between bays by closing affected bays promptly would be effective in preventing further spread.

Strengths and limitations of this study

- Provides an estimation of serial interval, and assessment of significance of patient proximity in spreading norovirus within hospitals.
- Different modelling approaches showed consistent results.
- A weakness is that although data collection were standardised it is often difficult to assess the accuracy of the information on patients' positions on a ward.

INTRODUCTION

Norovirus is the commonest cause of gastrointestinal infection worldwide.[1] There are between two and three million cases occurring each year in the UK.[2 3] Norovirus commonly presents as outbreaks of diarrhoea and vomiting and are frequently reported in hospitals, care-homes, schools and cruise ships.[4 5] Outbreaks in hospitals are disruptive, often leading to ward or bay closures, staff sickness and cancelled operations.[6] The cost of nosocomial outbreaks of norovirus to the National Health Service (NHS) in England was estimated at £115 million in 2002/2003.[6] Recently the cost in one region in Scotland was estimated at £1.2 million in the two norovirus seasons from 2007 to 2008.[7]

Understanding the benefits of infection control measures is challenging, because they are usually instigated as a package with several measures being implemented during an outbreak. While these interventions are based on sound infection control principles,

evaluating their efficacy in trials is difficult and the published literature on norovirus outbreaks does not provide clear evidence of the effectiveness of infection control measures.[5] In observational studies early ward closure has been shown to shorten the mean duration of outbreaks.[6 7] There is also evidence that vomiting and the resultant aerosols are important in transmitting the infection. People exposed to vomiting events, either by being close to the person who initially vomited, or by occupying the same area sometime after the initial event, have a higher infection risk.[8–11] However, these analyses are based on single outbreaks or events that led to subsequent disease. Improved understanding of how norovirus spreads in closed environments could lead to better infection control procedures.

The aim of our study was to assess how spatial proximity to a norovirus case is associated with risk of acquiring symptomatic norovirus gastroenteritis. Our hypothesis was that patients sharing bays (small self-contained areas within wards) with patients with symptomatic norovirus infection were more likely to become infected compared with those who were in another bay or part of the affected ward.

MATERIALS AND METHODS

Setting

We carried out enhanced surveillance of norovirus outbreaks from all in-patient wards in five tertiary care hospitals serving two cities in England, with a combined catchment of approximately two million people.

Surveillance data

We collected data during outbreaks from individual patients on date of onset of illness, symptoms (diarrhoea and/or vomiting), last date of illness for each patient, location on the ward at the time of the patients' symptoms onset (recorded as bed number and bay number) and also the ward type.

For two hospitals, information was recorded from January 2008 to November 2011 on specially designed forms that were completed by infection control staff and returned to the Health Protection Agency. Each month, we contacted the infection control lead at these hospitals asking about suspected or laboratory confirmed norovirus outbreaks and, if any had occurred and for the forms to be completed and returned. In three other hospitals the data were downloaded from a database on which infection control specialists had recorded these data items during outbreaks of norovirus occurring in the season of 2007/2008. Data from these three hospitals were downloaded during several visits to these hospitals. Data on outbreaks on norovirus were available from November 2007 to November 2011.

Patient location during outbreaks

We obtained ward plans for two of the five hospitals, which assisted in locating patients in the ward if only part of the information on patient location was recorded in the outbreak reports.

Definitions

Outbreaks were defined as two or more cases of diarrhoea and or vomiting of infectious origin in a ward occurring within 2 days of the first case suspected or confirmed to be due to norovirus. All the hospitals in this study used PCR for detection of norovirus in stool samples.

A bay is a small self-contained area within a ward. Usually bays contain between two and eight beds. Bays are not the same as individual single bed occupied rooms. Proximity was defined as patients who share a bay.

Analytical framework

The analysis is based on a probabilistic reconstruction of chains of transmission (trees) based on the dates of illness onset for patients affected in outbreaks. It makes use of methods developed for Severe Acute Respiratory Syndrome (SARS) transmission and later applied to norovirus.[12–15] If we knew with certainty who acquired infection from whom it would be straightforward to quantify the role of proximity in norovirus outbreaks, for example, by using regression analysis. However, in practice, transmission events are unobserved, so instead we consider all possible infection trees consistent with the data. We used a previously described approach to calculate the probability, π_{ij}, that patient i was infected by patient j for each pair of infected patients in each outbreak based on onset times and the serial interval distribution (the serial interval is the time from onset of symptoms in case i to case j), without using proximity data. The serial interval distribution tells us the probability of durations of 0, 1, 2… days between onset in a case and onset in secondary cases infected by this case. Given multiple possible sources for a case, we can use knowledge of this distribution to tell us how likely each is to be the true source. Full technical details are described in Wallinga and Teunis.[12]

We then used the matrix of π_{ij} values to simulate 1000 possible infection trees for each outbreak, by assigning the infector of patient i to be patient j with probability π_{ij}.

In these simulations, we assumed that the case with the earliest onset time was the index case and had no infectors on the ward. If more than one patient had the earliest onset date in a given outbreak, we selected the index case from these patients with equal probability in each simulation. For each outbreak k, we used these 1000 simulations to produce a proximity metric, P_k, defined as

$$P_k = \sum_{i,j,l} \frac{s_{ijkl}\, p_{ijk}}{1000}$$

where s_{ijkl} is equal to 1 if patient i was infected by patient j in simulation l of outbreak k and is zero otherwise. The p_{ijk} terms measure proximity between patients i and j in

outbreak k. In this application, we consider this to be a binary variable equal to 1 if patients i and j occupied the same bay at the time of first symptom onset of these patients. An overall proximity metric, P, is obtained by summing the P_k values. The value of P (and of P_k for individual outbreaks) should be interpreted as a measure of how much transmission occurs between patients in the same bay.

If people in the same bay pose a greater risk of infecting each other this will tend to lead to larger values of the proximity metrics, P, and P_k. We compared this observed metric with values obtained if proximity was not associated with transmission. This distribution was derived by performing random permutations of the bays of the patients in each outbreak and calculating P_k as above for each outbreak. These values were again summed to give an overall proximity metric, S, when proximity was by assumption not an important factor. We repeated this for 1000 random permutations of the patient bays to obtain 1000 sampled proximity metrics. These 1000 S values therefore represent a sample from the distribution of proximity metrics that would be expected if proximity played no role in spreading the disease during the outbreak. By comparing the 1000 sampled values of S with the observed value P we can evaluate whether transmission is more (or less) likely to occur between patients in close proximity. If proximity is unimportant the observed value of P would be unlikely to be in the tails of the distribution of S. If proximity leads to increased transmission the observed value of P would tend to be greater than most of the sampled S values. If proximity leads to decreased transmission (which could occur as a result of enhanced hygiene measures, eg,) the observed value of P is likely to be smaller than most of the sampled *S* values. Formally, we can perform a two-sided hypothesis test with a null hypothesis that proximity is not important where the p value is given by the proportion of sampled S values which are the more extreme than the value observed, P.

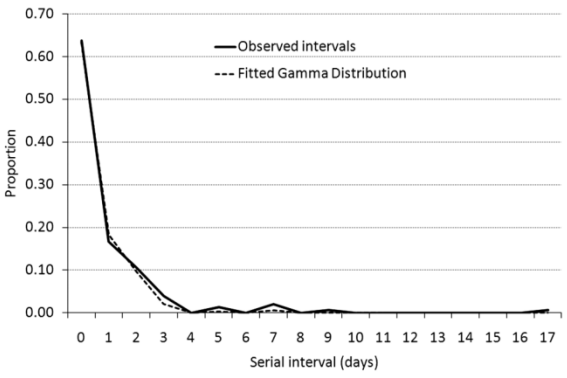

Figure 1 Serial interval distribution derived from onset dates of illness from observed outbreaks.

Serial intervals

A key input for constructing the transmission trees is the serial interval. Our best estimate came from the observed distribution of the difference between first and second onset dates for each outbreak, and our primary analysis made use of this empirical serial interval distribution. Often, more than one patient was ill on the first day of the outbreak, so we used the first date of illness onset in the next patient(s) for calculating the serial interval. This gave a mean serial interval of 1.86 days (median 1 day, 95% CI 1.6 to 2.2 days, obtained by bootstrapping).

We also performed sensitivity analyses using different assumptions. First, we used an estimate from a study of a community outbreak of norovirus at a scouting jamboree, giving a mean serial interval of 3.6 days, with an assumed γ distribution.[13] We then considered γ distributions with the same variance (4.1) but with the mean serial intervals varying between 0.5 and 5 days in half day increments. Data were analysed using R.[16]

RESULTS

Data were collected from 149 outbreaks in five hospitals between November 2007 and November 2011. These outbreaks affected 1694 patients and 456 staff. The average duration of the outbreaks, determined as the first date of onset to the last date of onset, was 8.9 days (median 8; range 1–40 days). Outbreaks affected an average of 11.4 patients (median 11; range 1–30) and an average of 3.2 staff (median 2; range 0–20). Data from these outbreaks gave a mean serial interval of 1.86 days. Figure 1 shows the distribution of serial intervals from the observed data and the nearest fitting γ distribution.

The spatial modelling analysis used data from 65 outbreaks where all data (for both onset dates and position in ward when taken ill) were complete. The outbreak characteristics were similar in these 65 outbreaks compared to the full dataset. The corresponding figures for these outbreaks were: average length of outbreak 9.5 days (median 8 days) average number of patients 11.9 (median 11) average number of affected staff 3.4 (median 2). The outbreaks affected various ward types, with most occurring in general medical wards (34%) and care of the elderly wards (28%). Other specialties were respiratory medicine (12%), stroke/neurology wards (11%), coronary care wards (9%) and orthopaedic/trauma wards (6%).

Proximity analysis

Figure 2 shows the observed proximity metric and the distribution of proximity metrics obtained under the assumption that proximity was not associated with transmission (from the simulated permutations). This shows how the proximity metrics observed relate to the distribution of proximity metrics if proximity was not important. The dashed line indicates the observed proximity metric (P) and the bars indicate the distribution of

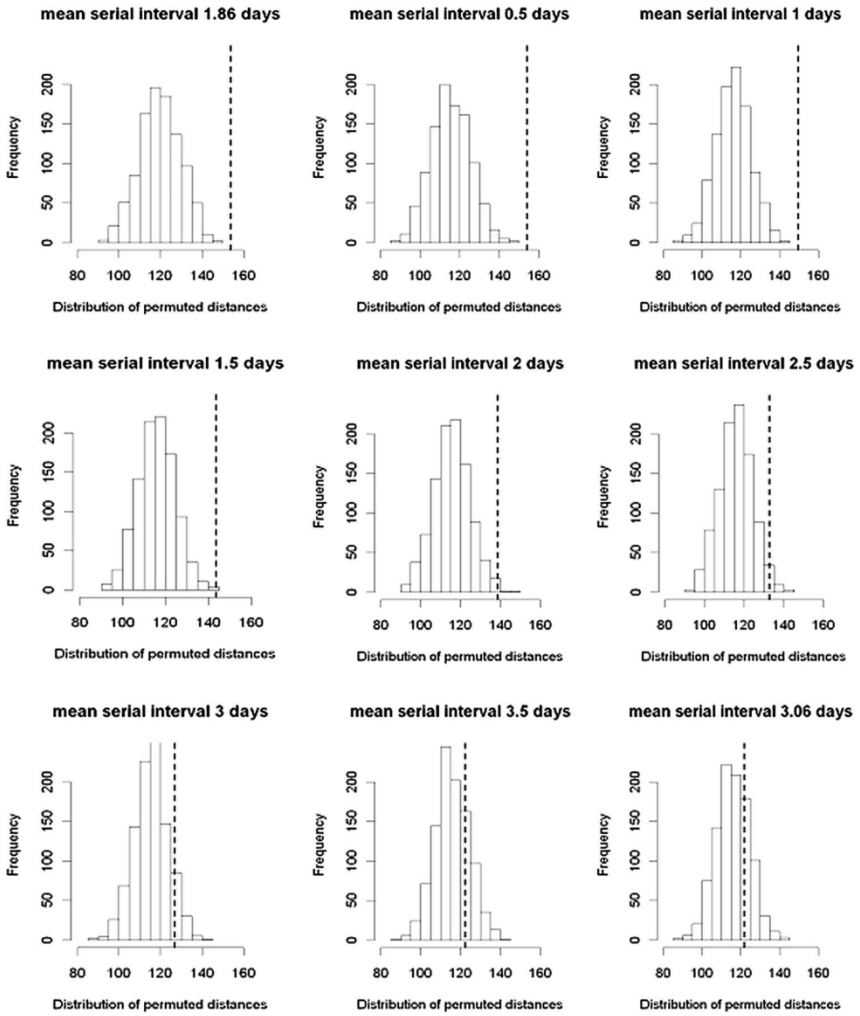

Figure 2 Observed (dashed line) and distribution of expected (bars) proximity metrics for each serial interval.

proximity metrics from the simulated permutations. For the model using the serial interval taken from the observed onset dates, the observed metric is outside of the range of the simulated distributions and is highly statistically significant ($p=153.34$, $p<0.001$). With serial intervals of less than 2 days proximity is either outside or at the extreme right of the simulated proximity metrics and the p values ranged from <0.001 for serial intervals of 0.5 days to 0.01 at a serial interval of 2 days. If we increase the assumed serial interval, the proximity metric moves to within the range expected from the simulated values, and at 3 days the p value was 0.2 (figure 2). Using the γ probability distribution derived from a community outbreak by Heijne *et al*[13] (mean serial interval 3.06 days), the proportion of observed proximity values fell within the range that would be expected if proximity were not important.

The results show that the proximity metric (P) was larger than would be expected by chance under the null hypothesis (that proximity is not important) up to a serial interval of 2.5 days ($p=0.05$).

DISCUSSION

We have detected a strong association where patients who are in the same bay as patients who become ill have a higher probability of themselves becoming ill compared with patients in a different bay. In other words, transmission of norovirus infections is more likely to occur among patients sharing a bay, compared with transmission among patients in different bays. While this might at first seem an obvious finding, there are competing theories about the transmission of the virus in complex healthcare settings. For example, transmission might occur through staff transferring virus on their hands or patients touching infected surfaces with their hands when moving around the wards or the hospital. The strength of our conclusion is sensitive to the

assumed serial interval distribution. We used values derived from the dates of onset of illness in patients during outbreaks on hospital wards. We also performed sensitivity analysis using a serial interval distribution derived from a study of norovirus in children.[13] However, because the degree to which this generalises to a hospital setting is unclear (intuitively the high contact rates in hospitals would be expected to lead to shorter serial intervals)[17] we explored serial intervals from 0.5 to 4 days, while constraining the variance. Our results show that for serial intervals of less than 2 days the observed effect of proximity (sharing a bay with someone else who was ill) is highly significant ($p<0.001$) and for serial intervals up to 2.5 days remained significant at the 5% level. This pattern was similar whether using the observed serial interval distribution from the outbreak data or using a parametric probability distribution.

Our study has some limitations. Although data collection were standardised it is often difficult to assess the accuracy of the date and place that patients were when they became ill. Specifically, accurate information on patients' positions on a ward was available for 44% of the outbreaks. The spatial analysis was undertaken on 65 outbreaks. In addition to the sensitivity analysis we also analysed the data by including outbreaks where onset dates of illness were complete but data on patient location were incomplete (where fewer than 10% of patient data on position was incomplete, 85 outbreaks). We dealt with missing values by allocating a completely separate bay for patients with missing data on location at time of onset. This approach is conservative in that it would underestimate the impact of proximity. Second, we removed the patients from the outbreaks if positional information was missing. Despite this limitation, the additional models indicated that that the results are robust to different assumptions about missing data which is evidenced by slightly higher probabilities obtained when using records with complete information only (see online supplementary table S1 and figure S1). As a check to demonstrate that the results were not an artefact of the statistical methods, we also ran the models on data where patient position was randomly assigned. This showed no pattern and the proximity measures were not significant for any of these models. In our analysis the estimation of Pk depends on outbreak size. However, we are not interested in the absolute values of P, only in how the value of P calculated with real proximity data compares with the value calculated with randomly generated proximity data (based on a permutation of the bay identities) which will be affected in the same way by outbreak sizes. We also performed a sensitivity analysis, normalising Pk by dividing it by the number of branches in the transmission tree for each network. This gives equal weight to each outbreak and allows Pk to be interpreted as the probability that two linked cases were in the same bay. This did not change the results of the analysis; the P metric still fell well outside of the measure one would expect from the random simulations ($p=0.004$, data not shown).

We used more than one approach to modelling the infection trees because of the lack of data on serial interval in norovirus outbreaks. Heijne *et al*'s method used data from child siblings at home. This was a useful starting point but is unlikely to be applicable to transmission in a hospital setting. Therefore, we derived γ distributions for serial intervals from 0.5 to 4 days. The average incubation period for norovirus is considered to be between 24 and 48 h.[1 4] In our analysis the serial intervals of up to 2.5 days is likely to be a more appropriate time period in a hospital setting, than the analysis from Heijne *et al*.

Molecular analysis of stool samples could more definitively link outbreaks, which can help to reveal transmission networks.[18 19] For example, in this study we have assumed that each ward outbreak was distinct, that is, all cases within a ward were part of a chain of transmission, but this may not necessarily be true. It is possible for multiple introductions to occur, and some outbreaks may have spread from one ward to another. Genetic characterisation of samples from each ward during possible multiple outbreaks of norovirus would shed light on transmission events and lead to further insight about the direction of transmission, including the possibility that the virus can be moved around the hospital.

Our study focused on patients rather than staff. Our hypothesis was that symptomatic patients who vomit are most likely to contaminate the area close to them and other patients in their vicinity. Obtaining data on staff movements is much more complicated and would only really be practical in a detailed prospective study.

The importance of spatial proximity in propagating transmission is consistent with other recent studies.[15 20] One study which used similar methods to calculate the infection trees[15] suggests that symptomatic individuals are likely to be the drivers of outbreaks of norovirus in hospital settings. Furthermore, the effective reproductive number was significantly higher for symptomatic patients compared with that for symptomatic staff. Norovirus transmission between people in close contact during sport, both within and between teams, has also been shown to occur[21] as well as airborne transmission through explosive vomiting.[22] One study demonstrated that successive staff working on an aircraft in which a member of the public had vomited also became sick.[11]

Norovirus has a low infectious dose[4 23 24] shedding virus occurs during episodes of vomiting, where the virus can become aerosolised and expose others in the vicinity. Therefore, closing the bay quickly, preventing movement to and from that bay and immediately paying attention to cleaning areas nearby to initial vomiting events are likely to be effective in preventing further spread. The index of suspicion for patients who become ill should be high and implementing infection control interventions should not be delayed until the results of sampling are received, because this would increase morbidity and prolong the outbreak. New guidelines on controlling outbreaks of norovirus in hospitals and care

homes recently released in the UK[25] move away from the need to close wards and operate on a 'manage within bays' principle. Our study has shown that patients in proximity to symptomatic patients are at increased risk of becoming infected by these patients.

CONCLUSIONS

We have shown a clear role of spatial proximity in the transmission of norovirus in hospital outbreaks. Increasing barriers to movement between bays by closing affected bays promptly would be effective in preventing further spread.

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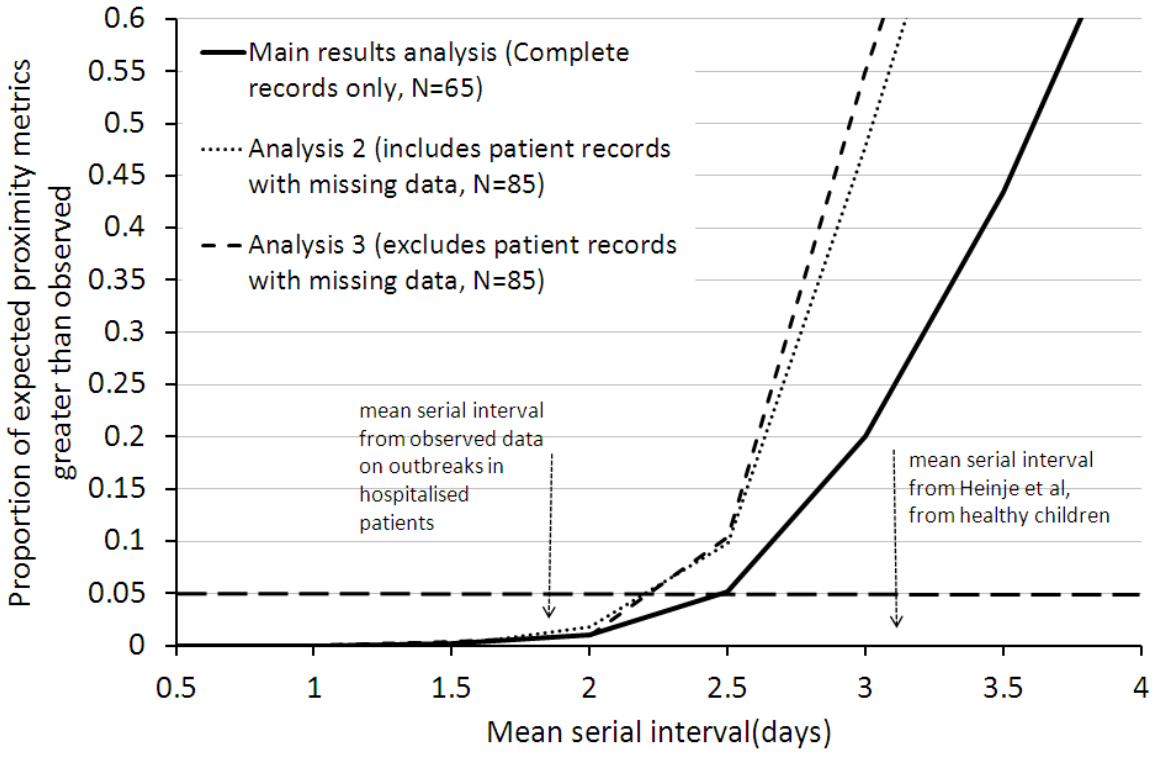
Supplementary information

Table 1 Modelling approaches used in the analyses.

Serial interval derived from observed data on onset dates from hospital patients during outbreaks (N=149)
Analysis 1: (main analysis in results) Include only outbreaks with complete data on patient position at time of onset. (N=65)
Sensitivity analyses
Analysis 2 Include outbreaks with missing values on patient position at time of onset. Patients allocated to distinct bays (N=85)
Analysis 3 Include outbreaks with missing values on patient position at time of onset, but exclude observations with missing values on patient position, i.e. Patients deleted from dataset (N=85)
Analysis 4 Remove all information on patient position and randomly allocate bays
Using gamma distributions of serial intervals from Heijne et al (From healthy population)

Figure 1_supplement. Comparison of results from modelling approaches, main analysis and sensitivity analyses.



R. Code.

This first part of the program creates functions that will be called in the main part of the program later on.

```
 # create the distance matrix function which codes 1 for patients sharing a bay and 0 for those in different bays
Makedistancematrix<-function(pid,bay){
 N<-length(pid)
 Dist<-matrix(data=0, nrow=n,ncol=n)
   For(i in 1:n){
     For(j in 1:n){
     If(i!=j & bay[i]==bay[j]) Dist[i,j]<-1
  }
}

Return(Dist)
}

# Create the simulated outbreak function this simulates one outbreak

Sim1outbreak<-function(pkl,onset.times.percase){
  N<-dim(pkl)[1]
  Number.of.possible.index.cases<-sum(onset.times.percase==min(onset.times.percase))
  Indexcase<-1+as.integer((number.of.possible.index.cases)*runif(1))
  Whoinfectswhom<-rep(NA,n)
  For(i in 1:n){
     Probnosource=max(1-sum(pkl[i,]),0)
     Source<-which(rmultinom(1,1,c(pkl[i,],probnosource))  ==1)
     If(source==n+1) source<-0
     Whoinfectswhom[i]<-source
     If(i==indexcase)  whoinfectswhom[i]<-0 # i.e. Infected outside
  }

  Return(whoinfectswhom)
}

# Create the function to randomise the bays in which patients are located
Permutebays<-function(bays){

 N<-length(bays)

 Return(bays[order(runif(n))])

}

# Create the function to calculate the infection trees

Calcoutbreakdist<-function(whoinfectswhom,Dist){
    Obdist=0
          For(i in 1:length(whoinfectswhom)){
          If(whoinfectswhom[i]!=0){
          Obdist=obdist+Dist[i,whoinfectswhom[i]]
                    }
```

```
        }
        Return(obdist)
}
# This section is the main program, it begins by reading in the data “data.csv” which is the comma delimited data file containing the data.
Dataset<-read.table("data.csv",header=T,sep=",")
#to ensure that the dates in the csv file are interpreted as dates by R
Dataset$dateonset<- as.Date(as.character(dataset$dateonset),"%d/%m/%Y")
S<-1000   # note this sets the number of simulated distance matrices to create
Numobks<-length(unique(dataset$obnumb))
Realcumulativedist<-rep(0,numobks)   # to calculate cumulative distance over all simulated outberak trees
Permuteddistances<-matrix(data = rep(0,S*numobks), nrow = numobks, ncol = S)
For(obnumb in 1:numobks){
Outbreak.id<-obnumb
Onset.times.percase<- dataset$dateonset[which(dataset$obnumb==outbreak.id)]
Unique.onset.times.percase<-unique(onset.times.percase)
Unique.onset.times.percase<-1+unique.onset.times.percase - min(unique.onset.times.percase)
N<-length(onset.times.percase)
Maxtimediff<-max(onset.times.percase)-min(onset.times.percase)
W<-rep(NA,maxtimediff+1)  #probability that the serial is i-1 days
W[1]<-0.6377
W[2]<-0.1678
W[3]<-0.1074
W[4]<-0.0403
W[5]<-0.0000
W[6]<-0.0134
W[7]<-0.0000
W[8]<-0.0201
W[9]<-0.0000
W[10]<-0.0067
W[11]<-0.0000
W[12]<-0.0000
W[13]<-0.0000
W[14]<-0.0000
W[15]<-0.0000
W[16]<-0.0000
W[17]<-0.0000
W[18]<-0.0067
W[19]<-0.0000
W[20]<-0.0000
W[21]<-0.0000
W[22]<-0.0000
W[23]<-0.0000
W[24]<-0.0000
W[25]<-0.0000
W[26]<-0.0000
W[27]<-0.0000
W[28]<-0.0000
W[29]<-0.0000
W[30]<-0.0000
Wij<-matrix(rep(0,N^2),nrow=N)
```

```
Number.of.possible.index.cases<-sum(onset.times.percase==min(onset.times.percase))
 For(i in 1:N){
  J<-1
  Onsettime<-onset.times.percase[j]
  While(onsettime<=onset.times.percase[i] && j<=N){

          Timediff<-onset.times.percase[i]-onset.times.percase[j]
      If(i!=j){
         If(i> number.of.possible.index.cases){
          Wij[i,j]<- w[timediff+1]
         } else {
           Wij[i,j]<-                                  w[timediff+1]*(number.of.possible.index.cases-1)/
(number.of.possible.index.cases)
         }
       }
      J<-j+1
      Onsettime<-onset.times.percase[j]
  }
 }

# denoms is the sum of likelihoods that person i was infected by person  i-1,i-2,...,1
Denoms<-c(NULL,rep(0,N-1))

For(i in 1:N){

    Denomfori<-0

    For(j in 1:N) {

     Denomfori<-denomfori+wij[i,j]

    }

    Denoms[i]<-denomfori

 }


Pkl<-matrix(rep(0,N^2),nrow=N)  #relative likelihiood  that k was infected by l

 For(l in 1:N){
  # print(l)
   For(k in 1:N){
    Numerator<-wij[k,l]
    Denom<-denoms[k]
    If(denom>0){
      Pkl[k,l]<-numerator/denom
    } else {
      Pkl[k,l]<-0
    }
   }
 }

For(i  in  1:number.of.possible.index.cases)  pkl[i,]<-pkl[i,]*(number.of.possible.index.cases-
1)/number.of.possible.index.cases
```

```
Pid <- dataset$caseid[which(dataset$obnumb==outbreak.id)] #This limits the variable pid to one outbreak

Bay <- dataset$bay[which(dataset$obnumb==outbreak.id)] #This limits the variable bay to one outbreak

Dist <- makedistancematrix(pid,bay)
   For (i in 1:S) {
   Oneoutbreaksim<-sim1outbreak(pkl,onset.times.percase)  #a possible reconstruction of outbreak - who infects whom.
   Realdist<-calcoutbreakdist(oneoutbreaksim, Dist)
   Realcumulativedist[obnumb]<-realcumulativedist[obnumb] + realdist
   Permd<-makedistancematrix(pid,permutebays(bay))  #this is for the permuted bays
   Distwithpermuteddistancematrix<-calcoutbreakdist(oneoutbreaksim, permd)
   Permuteddistances[obnumb,i]<-permuteddistances[obnumb,i]+
distwithpermuteddistancematrix
} # end for i in 1:S

Realcumulativedist[obnumb]<-realcumulativedist[obnumb]/S
Permuteddistancesalloutbreaks<-colsums(permuteddistances)
Test.statistic<-sum(realcumulativedist)  # for all outbreaks
Pvalue.2sided<-
2*min(sum(permuteddistancesalloutbreaks<=test.statistic)/length(permuteddistancesalloutbreaks),sum(permuteddistancesalloutbreaks>=test.statistic)/length(permuteddistancesalloutbreaks))

} #end for(obnumb in 1:numobks)

-----------------------------------------------------------------------------------------------------------
# Note this section can be used instead of the observed serial interval distribution if using the gamma distribution estimate of serial intervals

 W[1]<-pgamma(0.5,shape=shape,scale=scale) # probability of a serial interval recorded as 0 days (i.e. 0 to .5 days)
 For(i in 1:maxtimediff) w[i+1]<-pgamma(i+0.5,shape=shape,scale=scale)-sum(w[1:i])
-----------------------------------------------------------------------------------------------------------
```

Sample data.

Obnumb	Dateonset	Bed number	Bay	Caseid
1	22/12/2007	7	1	1
1	25/12/2007	5	3	2
1	25/12/2007	3	6	3
1	25/12/2007	6	1	4
1	26/12/2007	6	3	5
1	26/12/2007	3	1	6
1	27/12/2007	7	3	7
1	28/12/2007	4	1	8

Chapter 8. To close or not to close? Analysis of four years data from national surveillance of norovirus outbreaks in hospitals in England

BMJ Open

To close or not to close? Analysis of 4 year's data from national surveillance of norovirus outbreaks in hospitals in England

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ABSTRACT

Objective: To assess the impact of ward or bay closures, specifically, whether prompt closure of an affected ward shortens the duration of norovirus outbreaks and the resulting disruption in hospitals.

Design: Analysis of summary data from hospitals on outbreaks of norovirus from 2009 to 2012.

Methods: Using a large outbreak surveillance dataset, we examined the duration of outbreaks, duration of disruption, ward closures, the number of patients and staff affected and the number of lost bed-days, as functions of the timing of closure. We conducted Quasi-Poisson regression analyses to assess the effect of ward closure (timing of closure) on outcome measures, controlling for time of year (winter or summer), ward size and ward type (elderly care wards).

Results: Regression analysis indicates that after controlling for season ward size and type, the duration of outbreak and duration of disruption were shorter, fewer patients were affected by the time of closure and fewer patients were affected overall, when closure occurred promptly (within 3 days of the first case becoming ill) compared with non-prompt closure groups. However, in outbreaks where wards were not closed, the length of outbreaks were similar to the prompt closure group and also had fewer patients and staff affected and fewer cases per day of outbreak compared with prompt closure.

Conclusions: Closing a bay or ward promptly in an outbreak of norovirus leads to a shorter duration of outbreaks, a shorter duration of disruption and fewer patients being affected compared with outbreaks where wards were not promptly closed. However, the interpretation of these results is not straightforward. The outbreaks where the ward was not closed at all have similar characteristics in terms of the duration of outbreak and fewer people were affected compared with the baseline prompt closure group.

Strengths and limitations of this study

- A large standardised data set for analysis.
- This analysis provides a baseline should infection control strategies move away from whole-ward closures as the new guidelines suggest.
- A weakness is that analysis was carried out on summary data collected on outbreaks from a national web-based reporting scheme, which makes it difficult to unpick some of the questions around the ward characteristics which influence differences in the outcomes.

INTRODUCTION

Outbreaks of diarrhoea and vomiting due to norovirus are common in hospitals. These outbreaks can be disruptive, affect many patients and staff, lead to ward closures and cancelled operations due to staff sickness and lost bed-days. Norovirus outbreaks can occur at any time of year but most of the outbreaks happen during winter months, a time when there are increased competing demands for hospitals services.[1 2] Estimates for the cost of norovirus outbreaks vary between US$650 000 for a single outbreak in the USA,[3] £115 million nationally for England[4] and £1.2 million over a 2-year period in one region in Scotland.[5]

Evaluating the effectiveness of individual components of infection control measures is challenging, and the published literature on infection control measures do not provide definitive answers.[6] Measures introduced to control outbreaks, such as cohort or barrier nursing, enhanced cleaning, visitor restrictions and ward closures, are implemented concurrently, rather than individually. One observational study suggested that closing bays or wards within 3 days of the first person becoming ill shortened the length of norovirus outbreaks.[4]

Recent cost effectiveness and simulation studies[7 8] question the need for a complete ward closure. In addition, new multiagency guidelines in the UK on the control of norovirus outbreaks in hospitals and care homes

move away from a strategy of whole-ward closure to one of the managing strategies within bays.[9] Guidelines in the USA recognising the paucity of strong evidence suggest that the decision of ward closure should be based on risk assessment by infection prevention personnel. The categorisation of this measure in the US guidelines is described as a weak recommendation and that the evidence for ward closure is low quality.[10]

Using a large outbreak surveillance dataset, we aimed to assess the impact of ward or bay closures, specifically whether prompt closure of an affected ward shortens the duration of norovirus outbreaks and the resulting disruption in hospitals.

METHODS

Data sources

We used data from the national Hospital Norovirus Outbreak Reporting Scheme (HNORS), established by the Health Protection Agency (HPA) in 2009. This reporting scheme collects summary data on the outbreaks of diarrhoea and vomiting that occur in hospitals in England that are either laboratory confirmed or are suspected to be due to norovirus. Users of the system are provided with definitions in order to standardise the surveillance.

Outbreak definition

Outbreaks were defined as follows: *Suspected outbreak*: two or more patients who have either two episodes of vomiting or diarrhoea, or one episode of diarrhoea *and* vomiting, occurring on a ward within the hospital without laboratory confirmation. *A confirmed outbreak*: as above with laboratory confirmation of norovirus (where at least one specimen is positive for norovirus).

Most of the National Health Service (NHS) laboratories use either PCR or ELISA for detection of norovirus. For the purposes of reporting to HNORS, the HPA does not set minimum standards on what constitute laboratory confirmation; this is determined locally and it is accepted that an outbreak is laboratory confirmed if reported as such. Outbreaks on each ward are treated as distinct events. Outbreaks are considered over, if 7 days have elapsed following the last onset date of the last affected patient.

The reporting scheme is web-based and infection control teams based in the hospitals enter the data directly via a secure Internet database. Data items collected include first and last date of onset of illness, whether wards or bays were closed, dates of ward or bay closure, laboratory confirmation of norovirus, ward type, the number of patients or staff involved in the outbreak and the number of lost bed-days. The number of lost bed-days is the cumulative number of beds unavailable for use for each day of closure. The closure is defined as the restriction of new patient admissions, transfers into or discharges from the affected unit (ward or bay within the ward). Where a reporter chooses YES when answering the question on ward closure, they are then prompted to provide the date of closure and reopening. There is no option for NO and therefore leaving this blank assumes that no closure occurred.

Data analysis

The duration of outbreak was determined as the number of days between the date of onset of illness of the last patient and the date of onset of illness of the first patient plus 1 day (because the date after the last person was ill is the first date on which the outbreak had finished). The duration of closure was the number of days between the date of reopening the ward and the date of closing the ward. The duration of disruption was calculated as the number of days between the date of reopening the ward and the date of onset of illness in the first known case. Where there was no indication that the ward had closed (the question is left blank in the online form) we have assumed this meant there was no closure.

Outbreak reports from community settings (such as psychiatric units) or with no information on ward type were not laboratory confirmed, and single outbreaks that were recorded as involving multiple wards were excluded from the analysis.

Statistical comparisons

We examined the duration of outbreaks, ward closures and disruption, the number of patients and staff affected and the number of lost bed-days, as functions of the timing of closure. We also estimated the number of people affected on each day of the outbreak, calculated as the total number of people affected during the outbreak (staff plus patients) divided by the length of the outbreak (as defined above). We also used this measure to estimate the number of patients affected by the time the closure occurred. Outbreaks were classified into four groups (1) prompt closure, where closure occurred within 3 days of the first reported date of onset of illness, (2) closed between 4 and 6 days of the first reported onset date, (3) closed seven or more days after the first reported onset date and (4) not closed. Group 1, prompt closure, was the baseline group in our analysis. The 3-day cut-off for prompt closure was chosen because the only previous study showing any association with shorter outbreak duration used this cut-off and this seemed a reasonable hypothesis to test.

The data on all outcome variables were right skewed and transformation of the data did not normalise the data, so non-parametric tests were conducted to assess the differences between groups (Wilcoxon Rank Sum tests for two group analysis and Kruskal-Wallace tests for more than two groups). In the first instance, comparison between closure groups was conducted. However, factors such as size of the ward, ward type (elderly care ward) and time of year (winter) might be related to the duration of outbreaks and also affect the number of people affected during the outbreak, and confound the

relationship of the apparent impact of ward closure. Three groups for ward size were created (based on the distribution of the number of beds reported in each ward): small wards (≤16 beds), medium wards (17–27 beds) and large wards (≥28 beds). The comparison was made between medians because the data are skewed and this was a better measure than the mean.

We conducted Quasi-Poisson regression analyses to assess the effect of ward closure (timing of closure) on outcome measures, controlling for time of year (winter or summer), ward size and ward type (elderly care wards). Outbreaks where the ward size was missing are omitted from the regression model (eg, 16% of the outbreaks where no closure occurred). Quasi-Poisson regression provides more robust SDs than the standard Poisson regression methods where there is evidence of over dispersion in the model parameters. The model used was:

$$\log_e(Y) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_n x_n$$

where β_0=intercept, $\beta_1 x_1$=closure group, $\beta_2 x_2$=ward size group, etc.

The estimated outcome measure can then be calculated as:

$$Y = (e^{\beta_0})(e^{\beta_1 x_1})(e^{\beta_2 x_2})(e^{\beta_n x_n})$$

Backwards stepwise regression was carried out starting with a full model including all variables and interaction terms between variables. Variables that were not significant ($p>0.1$) were excluded from each of the models. We also tested for interactions between closure group and other factors. Interaction terms were excluded if the model was not significantly different from the model without the interaction term. The most parsimonious model including only variables that remained significant was used as the final model for each of the analyses. All analyses were carried out using R statistical software.[11]

RESULTS

Between January 2009 and December 2012, the HNORS received 5841 reported outbreaks of diarrhoea and vomiting. After exclusions (as outlined above) there were 3650 laboratory-confirmed norovirus outbreaks. Of these, 3437 (94%) could be categorised into closure groups (as defined above). Seventy-eight per cent of outbreaks fell into the first category. Table 1 shows the ward characteristics by closure groups. The closure groups were similar with regard to each of the characteristics. There was a little difference between the ward

Table 1 Ward characteristics by closure group

Ward characteristic	Closure group: Prompt closure N (%)	Closed in 4–6 days N (%)	Closed in 7+ days N (%)	Not closed N (%)
Ward type				
Elderly	614 (23)	65 (26)	21 (27)	92 (21)
General med	833 (31)	82 (33)	18 (23)	154 (35)
Admissions/short stay	241 (9)	11 (4)	3 (4)	31 (7)
Orthopaedic/trauma	189 (7)	13 (5)	5 (6)	29 (7)
ITU	7 (<1)	0 (0)	1 (1)	4 (1)
Respiratory/cardio	355 (13)	28 (11)	13 (16)	46 (10)
Gastroenterology	80 (3)	11 (4)	4 (5)	9 (2)
Diabetes/nephrology	120 (5)	9 (4)	1 (1)	21 (5)
Others	231 (9)	29 (12)	13 (16)	54 (12)
Total	2670	248	79	440
Ward size				
<17 beds	145 (6)	13 (5)	0 (0)	34 (9)
17–27 beds	1001 (40)	116 (48)	37 (49)	145 (39)
≥28 beds	1380 (55)	112 (46)	38 (51)	191 (52)
Total	2526	241	75	370
Year				
2009	419 (16)	33 (13)	18 (22)	74 (17)
2010	860 (32)	89 (36)	19 (24)	140 (32)
2011	538 (20)	61 (25)	16 (20)	104 (24)
2012	853 (32)	65 (26)	26 (33)	122 (28)
Total	2670	248	79	440
Summer/winter				
Summer	565 (21)	50 (20)	11 (14)	65 (14)
Winter	2105 (79)	198 (79)	68 (86)	375 (85)
Total	2670	248	79	440

ITU, intensive care unit.

characteristics, size and type of ward and year of outbreak and season (winter/summer) for each of the closure groups.

Closure versus non-closure

Analysis of closed versus not closed suggested that wards were more likely to remain open in summer χ^2=7.52 p=0.006, and small wards were less likely to close compared with medium or large wards χ^2=6.67, p=0.01. We did not find associations with other characteristics in this analysis.

Closure group analysis

The median duration of outbreak, duration of disruption and the number of patients affected were lower in outbreaks where there was a prompt closure compared with those outbreaks where it took longer period to close (table 2). However, the median duration of closure, staff affected and average cases per day of outbreak were higher in the prompt closure group (Kruskal-Wallace rank sum tests all p<0.001). Lost bed-days was not significant.

Regression analysis

Table 3 shows the results of the regression analyses. The models suggest that (after controlling for season, ward size and type) the duration of outbreak and total disruption was shorter and fewer patients were affected in the prompt closure group (group 1) compared with closure groups 2 and 3. The duration of outbreaks where closure occurred seven or more days after the first onset date are almost twice as long as those where closure is prompt (see table 3 and also online supplementary figure S1 appendix). The duration of closure was shorter and there were fewer cases per day in the other closure groups compared with the prompt closure group.

Outbreaks where wards were not closed had fewer patients and staff affected and fewer cases per day of outbreak compared with prompt closure (the baseline group) but there was no statistical evidence for a difference in the duration of closure.

Outbreaks occurring on larger units, on care of the elderly wards, were significantly associated with longer outbreaks, longer disruption and more cases in most of the models. The number of bed-days lost was not significantly associated with the closure group, but there was a positive correlation with increasing ward size and a negative correlation with care of the elderly wards. We found no evidence of interaction between closure groups and other factors.

DISCUSSION

We approached this study from the perspective of assessing whether disruption caused by outbreaks of norovirus can be mitigated by closing wards early. We found that in 80% of outbreaks reported, closure occurred promptly. This, on reflection, should not have been surprising given that the guidelines produced in 2000 recommended ward closure (and in these guidelines it was a strong recommendation) as one of the measures to control an outbreak of diarrhoea and vomiting.[12] However, these guidelines did not propose a time limit for closure. This was first recommended by Lopman *et al*,[4] and at the time this study was carried out, it was not evident that the closure occurred rapidly, at least not in the area in which the study was conducted.

In our analysis, we have some evidence of a dose response, whereby, closing a bay or ward promptly (within 3 days of the first case occurring) in an outbreak of norovirus, the duration of the outbreak is shorter compared with the outbreaks where closure is not prompt. The duration of the outbreaks was longer in the closure group where closure was delayed to seven or more days. Furthermore, when closure did occur promptly, fewer patients were affected and the total duration of the disruption (first onset date to when the ward is reopened) is also shorter. It might be argued that the prompt closure during these outbreaks was beneficial. However, the interpretation of these results is not straightforward. Outbreaks where the ward was not closed at all also have similar characteristics in terms of the duration of outbreak and fewer people affected compared with the baseline prompt closure group. These

Table 2 Median (and IQR) number of people affected and days of disruption by closure groups

	Closure group			
Outcome	**Prompt closure**	**Closed in 4–6 days**	**Closed in 7+ days**	**Not closed**
Duration of outbreak (days)	7 (4–9.75)	9 (7–12)	14 (10.75–18.25)	6 (4–11)
Total duration of disruption (days)	9 (6–12)	12 (9–14)	17 (13–20)	NA
Duration of closure (days)	8 (5–11)	7 (5–10)	7 (5–10)	NA
Number of patients affected	11 (7–15)	12 (9–16)	14.5 (10–18)	7 (4–11.75)
Number of staff affected	2 (0–5)	3 (1–6)	2 (1–5)	1 (0–3)
Bed-days lost	15 (7–38)	14 (7–43)	17 (6–46.5)	NA
Average cases per day	2 (1.3–2.9)	1.6 (1.2–2.2)	1.2 (0.8–1.8)	1.3 (0.8–2.0)
Number of cases by time of closure	2.4 (1.5–3.8)	7.0 (5.3–10.0)	11.0 (8.3–15.0)	NA

Kruskal-Wallace rank sum tests between groups were all significant p<0.001 except for lost bed-days.

Table 3 Regression model estimates for outcome by ward characteristic (figures in brackets are 95% CIs)

		Percentage increase/decrease over baseline by characteristic						
Outcome	**Baseline estimate from model†**	**Closure group 1 (not closed)**	**Closure group 2 (4–6 days)**	**Closure group 3 (7+ days)**	**Ward group 2 (medium)**	**Ward group 3 (large)**	**Elderly care ward**	**Winter**
Length of outbreak (days)	5.93 (5.59 to 6.30)*	4 (1 to 7)	32 (27 to 38)*	99 (87 to 101)*	11 (4 to 17)	22 (15 to 29)*	18 (15 to 21)*	7 (4 to 10)**
Length of closure (days)	6.79 (6.45 to 7.14)*	–	−13 (−9 to −17)*	−12 (−6 to −19)	17 (11 to 23)*	28 (21 to 35)*	18 (15 to 21)*	--
Total length of disruption (days)	7.62 (7.24 to 8.01)*	–	29 (23 to 34)*	82 (69 to 95)*	16 (10 to 22)*	23 (16 to 29)*	18 (15 to 21)*	--
Patients affected (number)	6.19 (5.89 to 6.52)*	−24 (−22 to −27)*	12 (8 to 15)*	24 (17 to 30)*	56 (48 to 63)*	86 (76 to 95)*	12 (10 to 14)*	10 (7 to 12)*
Staff affected (number)	2.01 (1.88 to 2.35)*	−47 (−42 to −52)*	12 (3 to 21)	16 (1 to 33)	29 (15 to 43)**	24 (11 to 37)**	--	29 (21 to 36)*
Lost bed-days (days)	13.44 (11.54 to 15.65)*	–	5 (1 to 15)	24 (6 to 44)	85 (58 to 117)*	129 (96 to 167)*	−17 (−12 to −22)*	--
Cases per day (number)	1.74 (1.64 to 1.85)*	−24 (−21 to −28)*	−22 (−12 to −26)*	−43 (−37 to −49)*	37 (28 to 46)*	39 (31 to 64)*	−8 (−5 to −11)**	--
Cases by close (number)	2.15 (2.00 to 2.32)*	–	176 (165 to 186)*	302 (282 to 322)*	42 (31 to 53)*	40 (30 to 51)*	--	--

*p<0.01 **p<0.05.
†Prompt closure (closure group 0≤3 days) in small ward (ward group 1) -=not closed, --=not significant (excluded from the model).

findings might suggest that there is no compelling evidence that closing the ward is an effective way of curtailing an outbreak of norovirus.

There are limitations to this study. The analysis was carried out on summary data collected on outbreaks from a national web-based reporting scheme. During data entry, there are some built-in data validation steps, but despite this it is difficult to validate all of the data entered and we have to accept that there might be some errors. For example, where there was no information on closures (where the reporter has not selected YES at the question on whether the outbreak led to closure), we have assumed that the ward did not close. It is conceivable that in some of these outbreaks closures did occur. In this case, the outcomes in this category (not closed) might have been more favourable to this group, especially if the ward closed promptly.

It is also difficult to unpick some of the questions around the ward characteristics that make for differences in the outcomes. For example, outbreaks where wards were promptly closed might have been shorter because they were in smaller wards and therefore were shorter simply because the pool of susceptible patients was small. We also assumed that all other aspects of infection control, including increased hygiene measures, are carried out during outbreaks and that these procedures do not differ between outbreaks.

The current guidelines suggest that wards are reopened following terminal cleaning, which is normally after 72 h after the onset of the last known case. However, we have to accept that, in some circumstances, this might have to be altered in order to respond to situations, for example, if there have been a number of ward closures and there is pressure for hospitals to reopen to provide services. We have excluded from the analysis outbreaks on some wards which cannot close (eg, intensive care units) for operational reasons, so these will not have skewed the results. Furthermore, each outbreak was limited only to one ward, because we ask for outbreaks on each ward to report separately, and this might not have been the case for every outbreak. Although we were able to exclude outbreaks where it was clear from the report that the outbreak involved more than one ward, it is possible that some outbreaks spread from one ward to another. In this case, our estimate of the duration of the outbreak might be shorter than the actual event. The current approaches to collect samples during outbreaks of norovirus, where several samples are collected from the beginning of the outbreak and subsequent cases are not always sampled, militate against answering the question about spread between wards. Methods have been developed which can determine these transmission events[13 14] and it is now possible to show if the virus has been passed from one person to another or if patients have contracted the virus from separate introductions. In order to understand the transmission events and the way in which the virus can spread throughout a hospital, a dedicated study would be needed where samples are taken from patients who fall ill on each ward, along with more detailed data on onset times and position on the ward when the person became ill.

The analysis of number of cases per day (although limited because it is essentially an average) suggests that some outbreaks were 'slow burning' in which there are a just a few new cases occurring each day of the outbreak. This might explain the differences in the data, whereby the longer it takes to close a ward the longer the outbreak lasts and more patients are affected overall. In all outbreaks where closure occurred, the duration of closure is similar, suggesting that the act of closing is beneficial contributing to curtailing the outbreak. The number of cases occurring during an outbreak might not follow an even progression, sometimes several cases can come to light on 1 day and 1 or 2 days elapse between the next cases. However, it is not possible to tell this from summary data; again one would need more data on individual onset dates and the number of new cases on each day of the outbreak and this would require an observational study. Norovirus has a short incubation period and the estimated serial interval is short (possibly around 2 days)[15] so it would not be unreasonable to expect many cases to occur in the first few days of an outbreak.

For our analysis, we had a dataset considerably larger than that used in the study by Lopman *et al*. A major difference with our data is the finding that, in the majority of outbreaks, wards were closed within 3 days. In the study by Lopman *et al*, the wards that were in the prompt closure group accounted for only 14% of the outbreaks analysed. Moreover, the non-prompt closure group was comprised of outbreaks where wards were not closed and those that closed later than 3 days.

We also restricted our analysis to outbreaks that were laboratory confirmed as due to norovirus; therefore, it is unlikely that these outbreaks would have atypical characteristics to those not associated with norovirus infections. What is evident from our analysis is that ward size and elderly care wards had an independent effect on the length of outbreaks. Lopman *et al* found that the number of beds on a ward and elderly care wards was related to an increased hazard of outbreaks occurring.[2]

Our analyses have implications for the control of norovirus in hospitals and other closed settings such as care homes. The finding that larger ward size is associated with increased duration of outbreaks fits in with other studies which suggested that enclosing bays and putting doors on bays were beneficial and shortened the duration of outbreaks.[7 8]

In the USA, outbreaks in hospitals are rarely reported and hospitals tend to have single or double occupied rooms rather than large wards. The notable feature in a large hospital outbreak reported in the USA was the high ratio of staff to patients affected and the higher attack rates in staff compared with patients.[3] Patients are more likely to spread norovirus infections during

outbreaks in enclosed settings rather than healthcare workers[16] and there is good evidence that proximity of patients to one another[15] and vomiting are the likely principle driver of outbreaks.[17 18] Furthermore, the time it takes for an infected person to infect another shortens as an epidemic unfolds.[19] In a ward with many beds, it is easy to see how this could cause an outbreak to infect a large number of patients. If bays were enclosed with solid physical barriers such as doors and floor to ceiling walls, this effectively creates small rooms in which onward transmission can be more easily prevented.

Is it still reasonable to suggest that closing a ward or bay is an effective tool in curtailing an outbreak of norovirus? It has been previously shown that it is difficult to evaluate the effectiveness of individual infection control methods.[6] It is likely that they are effective only when introduced together (in today's parlance as a bundle). One aspect of infection control is closing an affected area and reducing the risk of further exposure to other patients. Taking the decision to close an area is a tacit indicator to staff working in the area and serves to heighten the awareness of a problem and the need to implement infection control procedures. Leaving a ward open while patients are symptomatic increases the risk of exposing newly admitted patients. If these newly exposed patients are subsequently moved to another part of the hospital, they are likely to contribute to onward transmission. The duration of closure was similar in all of the closure groups, suggesting this is an effective strategy particularly in larger wards, and during winter when outbreaks are more common.

What this analysis of the HNORS data provides is a baseline to judge how outbreaks of norovirus might unfold should hospitals begin to change their infection control strategy away from whole-ward closures as the new guidelines suggest. One of the strengths of surveillance data is its sustainability which allows for continuous collection of consistent data relatively cheap. Continued monitoring of the HNORS data in the future, in light of the recent changes to the guidance, would show if the burden of norovirus outbreaks changes, particularly in terms of increased duration and patients affected.

Conclusion

A prompt action is required in order to help control outbreaks of norovirus. However, more detailed studies can help to unravel the complexities around ward characteristics and help to explain why some outbreaks tend to come to an end without further action. This would entail collection of information on ward type, number of cases on each day of the outbreak, position in the ward when the patient became ill, whether the patient had been moved in the 24–48 h prior to symptoms and how many patients had become symptomatic before the closure.

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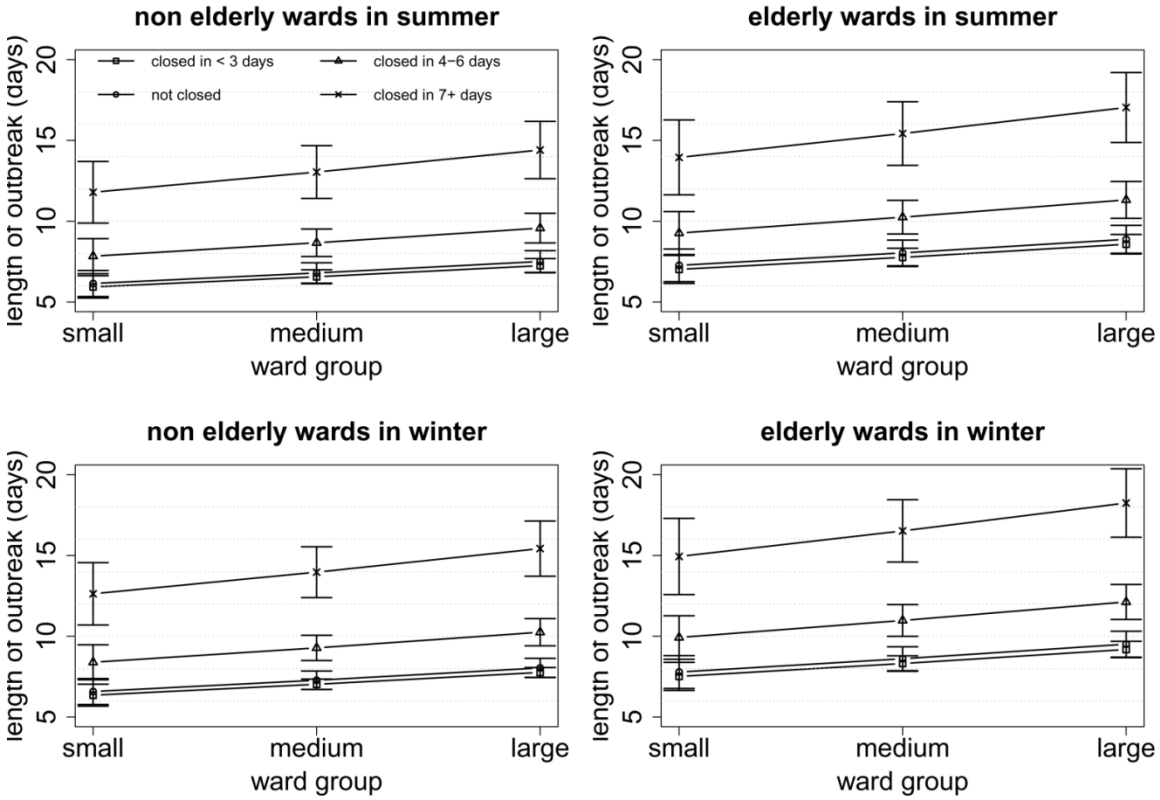
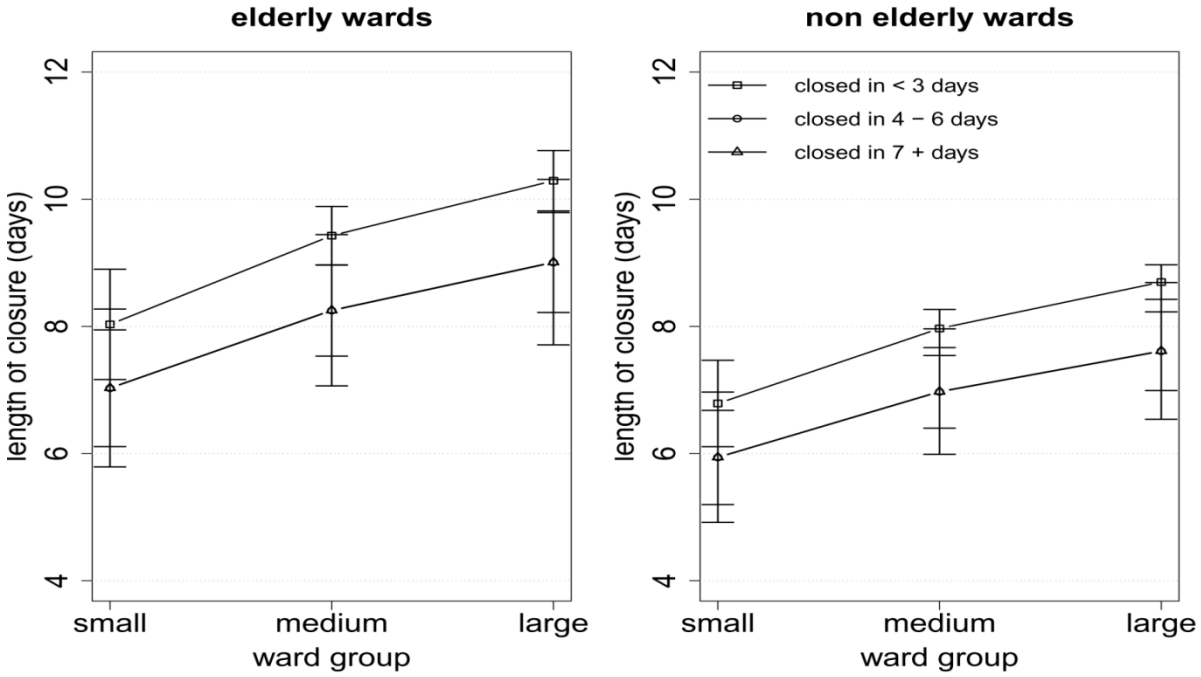
Supplementary information

Figure S1 appendix

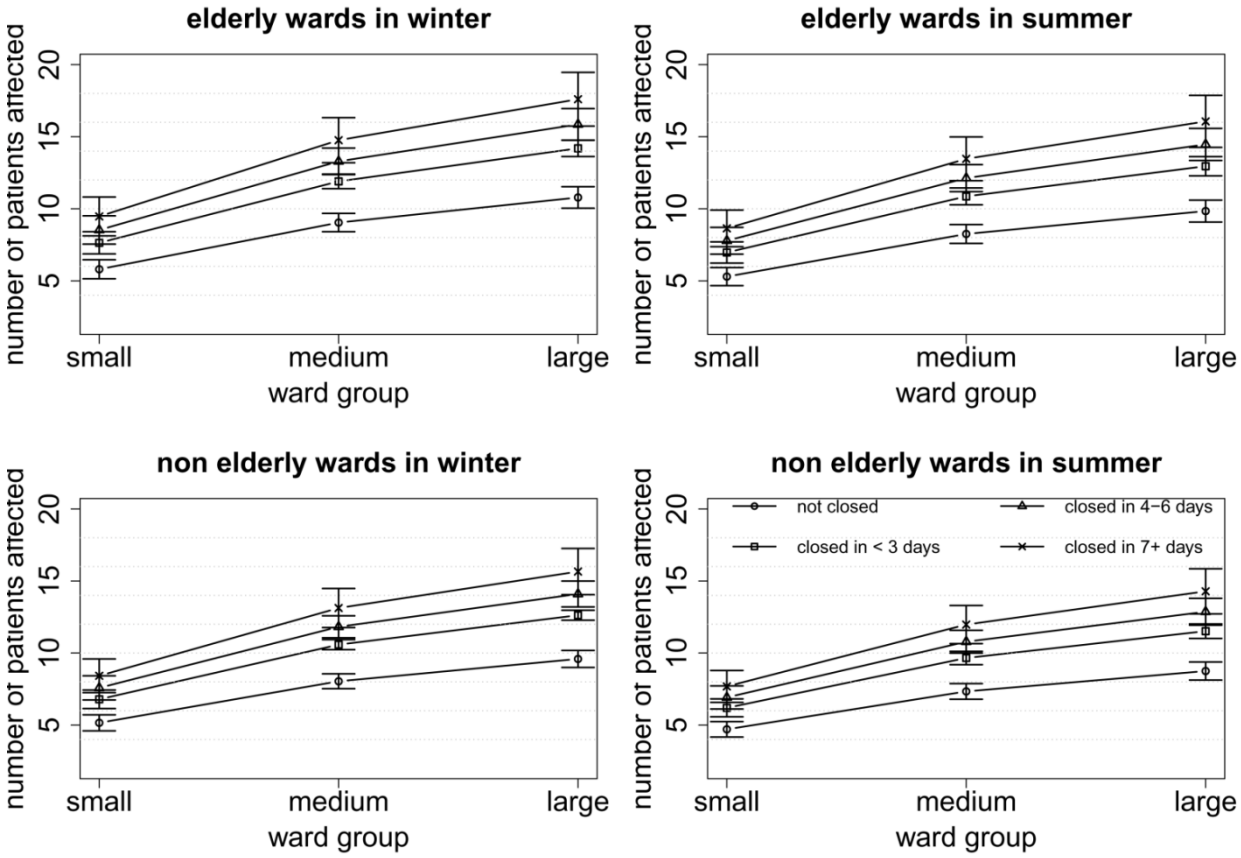
Duration of outbreak by closure group and elderly ward/winter



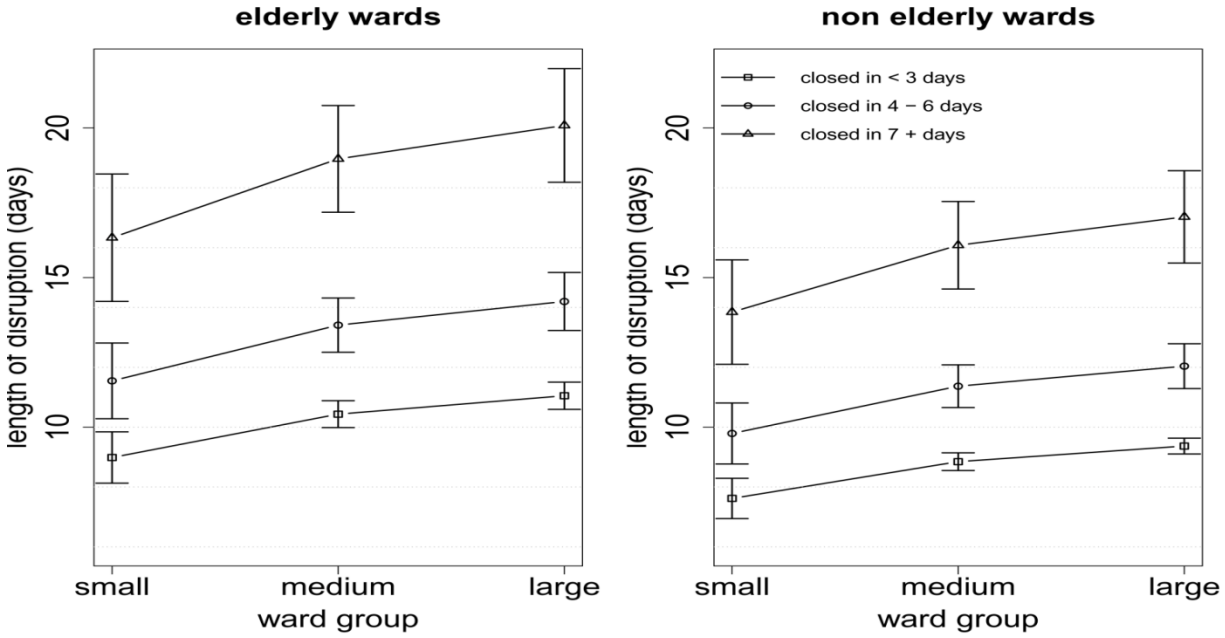
Duration of closure by closure group and elderly wards



Number of patients affected by closure group and elderly wards/winter



Lost bed days



Chapter 9 Overall discussion

In this thesis I have explored in depth the epidemiology of norovirus in hospitals. I have done this through a series of inter-linked studies that explored mortality, morbidity, transmission pathways and aspects of infection control.

One of the main challenges posed by norovirus infection remains public health surveillance of a mild and, therefore, grossly under-reported illness. Using a modelling approach, the importance of norovirus-related mortality is demonstrated. The investigation into the possibility of a link between mortality and norovirus infections was prompted by the finding from Lopman *et al* that hospital patients appear to suffer worse outcomes, in terms of recovery, compared with patients in care homes. This paper demonstrated an association between mortality in the elderly and norovirus infections. This is the earliest publication showing an association between mortality and norovirus infection. There have been some publications since this one that have also demonstrated a link between mortality and norovirus, one in the Netherlands [1] and one in the United States [2]**.**

The number of deaths associated with norovirus in the paper in this thesis was estimated at around 80 each year in England. This increased in years where there was higher norovirus activity. Norovirus activity can increase as a result of changes in the virus structure [3-6] leading to emergent strains. From analysis presented in chapter 3 the increased number of deaths, in years where there was known to be a new variant GII.4 virus in circulation, was not attributed to changes in the virus making it more pathogenic , but as a result of increased number of cases overall.

A direct causal link between norovirus infection and death is difficult to show, but what this paper highlights is that, in some populations, infection with norovirus is not a trivial disease. Given that the population structure in Britain is changing, with the proportion of people in the

over 65 age group increasing, this means that in future there will be more vulnerable people and, therefore, greater numbers of deaths associated with norovirus.

As with all modelling approaches there are some assumptions that are made within the model that require discussion. First, during the period for which the data were used it is possible that testing policies and, or, reporting behaviour changed. If the proportion of laboratory reports of norovirus diagnosed by PCR increased this would increase the sensitivity of detection. Thus the decrease in the ratio of deaths to laboratory reports in 2002/2003 might be due to either increased testing or norovirus identification. Secondly, the modelling approach can also underestimate how much of the seasonal variation in mortality is really associated with norovirus laboratory reports (and also non-seasonal pathogens). There was a considerable background (non-seasonal component) in the models.

Having demonstrated an association with mortality and norovirus, this posed the question of whether there is a measurable level of morbidity leading to a requirement of medical treatment. Most of the literature on norovirus suggests that it is a mild self-limiting illness, which does not require contact with medical services. This was investigated using similar modelling methods to establish an association between norovirus infections and hospital admissions.

In this short paper (chapter 4) it was estimated that around 9% of elderly and 5% of adults (those aged 18 and over) who had a diagnosis of unspecified gastroenteritis this diagnosis was attributed to norovirus infection. For the elderly over 19% of these diagnoses was attributable to norovirus in the busier weeks of the norovirus season.

Using the Hospital Episode Statistics (HES) codes, which specifically recorded norovirus infection, and adding to the predicted number of admissions for norovirus hospitalisations from the models, it was estimated that norovirus accounted for 1.2 per 1,000 admissions in the elderly and 0.6 per 1,000 admissions in adults. This added up to an estimate of around

3,000 hospital admissions each year in those over 18 years of age because of community-acquired norovirus infections.

There was a clear increase during the peak weeks where norovirus activity is highest. The estimate in this paper was much higher than previously estimated [7,8] based on reported hospitalisations from outbreak reports from general surveillance of gastrointestinal diseases. The assumption from this modelling is that all of the cases admitted were admitted from the community, although it is still possible that some of these cases could have acquired their infection whilst already in the hospital. The HES code is assumed to have been correctly attributed. Nevertheless, this still represents a significant and important method of introduction of norovirus into hospitals from the community, which, given the infectivity of the virus, has the potential to seed many outbreaks.

Outbreaks of norovirus are commonly reported in hospitals. The paper on the surveillance of norovirus outbreaks in hospitals (chapter 5) sheds light on the burden that these outbreaks cause hospitals in the NHS in England. The occurrence of outbreaks of norovirus in hospitals has been recognised for over thirty years [9]. Analysis of the surveillance data on general outbreaks of gastrointestinal diseases showed that norovirus was the most frequently reported cause of outbreaks, and that these outbreaks were most commonly reported in health care settings. The development of a reporting system tailored specifically at recording outbreaks of norovirus in hospitals was able to provide additional insight on the burden that norovirus imposes in hospitals. The system was developed with standardised definitions, which means that the reliability of comparisons between hospitals is increased.

In the first two years of the new surveillance scheme launching nearly 4,000 outbreaks were reported. These outbreaks led to 40,000 patients and over 10,000 staff becoming infected with norovirus. The disruptive nature of these outbreaks was shown in that 70% or more led to ward closures. There is little evidence that the epidemiology of norovirus outbreaks

changed from one season to the next, with the average duration of the outbreaks, number of patients and staff affected not differing over the last two seasons.

This is an interesting finding given that in the 2009/2010 season saw the emergence of a new strain of norovirus [6]. In this winter season there were more outbreaks recorded than the following season. Because the HNORS system was not running before the winter of 2009 it cannot provide comparisons to seasons earlier than this. However, laboratory reports of norovirus were clearly elevated in that season compared with the seasons prior to this and following 2010/2011. The hospital outbreak reporting scheme is voluntary, so inevitably there will be some under reporting of outbreaks. In order to try to assess the level of under reporting a comparison with laboratory data from Specialist Centres in PHE was carried out. This was in the form of a capture re-capture analysis. This led to the assessment of under reporting of around 20 percent. The capture re-capture method is not without difficulty. It is not possible to assume that the two systems are completely independent and thus the likelihood that capture in one system is related to the other could affect the reliability of the results. In the absence of any other source of data this is the only comparison that could be made. This surveillance and the subsequent analysis provided the first reliable evidence of burden of norovirus in hospitals in England, not merely in terms of the number of outbreaks, but in terms of the number of people affected, and the level of disruption this leads to in terms of ward closures. This surveillance scheme also provides policy makers with information, which can help to direct where there is a need to provide resources for further research.

Controlling outbreaks of norovirus is challenging, and this is particularly a problem in hospitals, an environment where people are in close confinement, and where people are constantly moving around. New patients are admitted daily, which provides a constant pool of newly susceptible people, and staff move frequently from one ward to another. Visitors traverse communal areas before and after visiting wards.

The earliest guidelines on controlling outbreaks of diarrhoea and vomiting in hospitals suggested that only one of the infection control practices were based on experimental scientific evidence [10]. A review of the literature to ascertain whether this situation had changed was conducted. The review was not limited to hospitals, and considered other settings, but did exclude outbreaks that were food borne in origin. The review identified over forty published papers, providing reports on over seventy outbreaks; some papers reported more than one outbreak.

The results of review showed that outbreaks in healthcare settings were longer than in other settings, although this is likely to be explained by self-censoring. So outbreaks in other settings are limited in length because people do not spend long periods of time in those settings. Comparing outbreaks according to whether or not infection control measures were implicated did not show measurable differences in attack rates or duration of outbreak. The conclusion was that the published literature did not provide evidence on the effectiveness of infection control measures. However, it also showed that a serious limiting factor was that the published literature lacks standardisation in the way outbreak investigations are reported. This lack of standardisation could have led to the misclassification of outbreaks. Where outbreak reports did not specifically mention infection control measures, they were assumed not to have been instigated and therefore, could have affected the analysis.

One of the limitations of the review was that only one reviewer identified the articles for review. The reviews were limited to those published in English and mostly indexed in Pub Med. Although grey literature was searched no articles were identified. Publication bias can strongly affect which outbreak investigations are published, but this normally produces biases which identify strong effects.

The finding that the published literature did not provide clear evidence of the effectiveness of infection control measures prompted analysis of outbreak reports in hospitals to address the question of whether early closure during outbreaks is beneficial (chapter 7). The study in

Avon [11] suggested that this might be the case. However, there has been some question about the strength of this evidence. In recently produced guidelines [12] the idea of managing patients within bays was introduced and other studies [13,14] also suggest alternative approaches to ward closures.

The findings from the analysis of over 3,000 outbreaks reported to the hospital outbreak reporting scheme did suggest that there was some benefit. There was a difference in the experience of outbreaks where closure was not prompt. Those outbreaks in which wards that closed more than three days after the first person became ill, had longer average durations of outbreak and more patients affected compared with wards where closure was prompt. However, the duration of closure was similar regardless of whether or not wards were closed promptly. Winter time, larger wards and elderly care wards were associated with increased duration of outbreaks. Elderly care wards were associated with fewer bed days lost and cases per day.

What is intriguing is that the duration of closure was similar, regardless of whether or not the ward was closed early in in the outbreak. Some outbreaks only lasted a short time even though wards remained open. The data from this analysis did suggest that wards were more likely to remain open in the summer - a time when norovirus activity is lower. Small wards were more likely to remain open than larger wards. These could have had an effect on the nature of the outbreaks but this is difficult to argue with any certainty. This uncertainty is largely because the data analysed are summary data on outbreaks. This means it is difficult to unpick other complications or confounders, such as bed turn over, case mix, and the effect that newly emergent virus strains might have in affecting outbreaks.

An interesting finding was that the majority of wards closed quickly. This is quantitatively different from the experience of Lopman *et al* when they undertook the study in Avon. One similarity between this study and that of recent studies [13,14] was the finding that smaller ward size leads to shorter outbreaks and less disruption, with fewer people affected and shorter

time to get the ward re-opened after the start of the outbreak. The length of closure was similar in the closure groups, whether closed promptly or not. This might suggest that closing the ward is another strand to ramping up infection control measures. Although ward closure is disruptive in itself, the duration closure occurs is not necessarily longer if wards are closed quickly. This strategy is likely to benefit larger wards in particular and during winter time.

Given the suggestion from the literature that vomiting plays a role in the spread of norovirus [15-19], an enhanced surveillance programme was set up. The aim of this was to look into whether proximity of patients to one another was a possible driver of outbreaks of norovirus in hospitals.

In this study (presented in chapter 8), during outbreaks of norovirus, information was collected on the date and time of onset of illness in patients (and staff), the position on the ward the patient occupied when they became ill, when the symptoms stopped. From this information it was possible to construct infection trees using a probability model (who infected whom) based on a method developed for the Severe Acute Respiratory Syndrome (SARS) [20] epidemic and adapted later for norovirus [21,22]. Once it has been established who is likely to have infected whom, it is possible to construct a statistical test to see if there is an association with proximity. In this study proximity was defined as those patients who shared a bay. There was strong evidence to suggest that patients sharing a bay were at higher risk of contracting illness, compared with those in a different bay. If the alternative explanation for spread (e.g. Staff transferring virus through close contact with patients) was more important the impact of proximity would not have been so clear cut. This study also estimated the serial interval (time from infection in patient 1 to infection in patient 2). Both of these findings are novel. Although other researchers have suggested that ill patients are more likely to transmit norovirus compared with members of staff [23], this study also shows that this is likely to be due to the proximity of patients to one another. It is likely, therefore, that vomiting and aerosolised virus particles are of particular importance.

The limitations of this study, a particular problem from the enhanced surveillance, included the inability of infection control staff to collect and report accurately the position of patients on the ward when they became ill. Also the date and time at which patients were ill was not always available. Only 44% of the reported outbreaks could be used for analysis, where there was complete information on both timing of illness and position on the ward. It was also assumed that patients involved in outbreaks on each ward were all part of one transmission chain. It is possible that norovirus can be introduced on one ward by more than one person, and that transmission could occur from one ward to the next. However, despite these limitations and the strength of the association that was found in this study, and given the infectiousness of norovirus, it does provide good evidence that interventions are best carried out quickly.

Conclusions and recommendations

These studies have shown the importance of norovirus as a public health problem in hospitals. Despite most people not attending medical services a considerable number of people are admitted to hospitals and a measurable degree of mortality are associated with norovirus each year. The number of outbreaks that hospitals have to deal with is considerable. Although infection control measures that can be put in place are largely the result of expert opinion, it has been possible to show that some controls would be successful in mitigating outbreaks.

It is still difficult to carry out accurate surveillance of norovirus. Because norovirus is a short term illness and most people do not contact medical services accurate measurement in terms of counting cases is unfeasible. Attempts have been made to use syndromic surveillance to measure increasing norovirus activity with limited success [24]. The problem with this approach is that syndromes are not necessarily condition-specific and changes to the algorithms used in the system can alter the signals of some syndromes.

Recommendations arising from the thesis

One of the questions that it was not possible to address from the studies employed was tracking virus spread from person to person. There are at least two aspects that are required to improve tracking of norovirus during outbreaks of norovirus in hospitals. First, more resources are required for collecting information as the outbreak unfolds. One of the difficulties of the enhanced surveillance was the inability to collect accurate data on outbreaks. Larger outbreaks tended to be more problematic because, as the outbreaks unfolded, collecting information was more difficult.

This would mean better resourcing of infection control teams and making better use of information technology. One solution might be to introduce an electronic ward round system such as that introduced to improve the management of *Clostridium difficile* [25] Secondly, improving diagnoses during outbreaks requires a change in the attitude towards collecting samples for microbiological analysis. In the enhanced surveillance study it was not possible, despite attempts, to obtain stool samples or the results of stool samples along with the outbreak information. This hampered the attempt to track outbreaks within wards, and to link outbreaks in different wards.

At present the system seems to be based on the regime developed under the era of electron microscopy. That is, samples are taken when several patients are ill and once norovirus is diagnosed further sampling (even on other wards) tends not to be carried out. This seriously limits the ability to ascertain whether outbreaks on other wards are due to norovirus but can allow for other pathogens that might coincidentally cause outbreaks of diarrhoea and vomiting.

There have been documented outbreaks of diarrhoea and vomiting involving *Salmonella* spp. [26-28] so norovirus is not the only cause of this type of outbreak. In one of these several patients died and occurred at the time when norovirus activity would normally be increasing.

Similarly in a study of gastrointestinal disease outbreaks in long term care facilities in Australia [29,30] bacterial causes were found to contribute to a number of outbreaks. This is an important fact to highlight because the control of outbreaks of salmonella and other bacterial causes would tend to focus on food borne sources. Norovirus can be introduced on foods but due to its infectivity person to person spread is more likely to occur.

In light of this a change in the attitude to testing of diarrhoeal specimens is recommended, firstly to be assured that what is being observed is norovirus, and secondly when outbreaks of norovirus are detected, continuous monitoring of specimens would assist in outbreak tracking and identifying infection control breakdowns.

Given that this study has shown the importance of proximity in spreading norovirus it would be important to include infection control specialists in the design of ward layouts when new hospitals are built or older ones refurbished. Also specifically designing hospitals with more single and double occupied rooms instead of large wards would help prevent the spread of norovirus.

Recommendations:

- Increased resources for infection control teams
    - Improved data collection as the outbreak unfolds
    - Introduction of electronic ward rounds
- Improve diagnostics during outbreaks
    - Increased sampling of patients during outbreaks to help track outbreaks
    - Ensure that the cause of an outbreak is properly identified
- Include infection prevention and control specialists in ward/hospital design during modernisation work or new hospital building.

Recommendations for further research

One of the limitations of this study was the inability to track norovirus outbreaks. The ability to sequence norovirus to a high resolution to distinguish multiple introductions as opposed to on-going transmission leads to the possibility of setting up specific studies in order track outbreaks. This would involve detailed collection of data on onset times of illness, position in the ward when ill, and location of the patient in the 24-48 hours prior to onset of illness. Taking more samples during outbreaks would be needed. This would entail taking samples at the beginning and sampling from additional patients as the outbreak unfolds for more detailed specialised analysis in the laboratory. This is likely to provide answers such questions about on-going transmission and identifying events that might have led to the spread of norovirus from one ward to another.

It was not possible in these studies to determine why some outbreaks were short and infected only a few people, whereas others were much longer affecting more people. Collecting detailed data on outbreaks, as outlined above, could also give some clues as to whether some genotypes are more likely to cause protracted outbreaks than others. This might be useful information for infection control because rapid detection and identification of genotypes that appear less pathogenic (less likely to cause large outbreaks), might be informative because they might be dealt with by less disruptive infection control measures.

A further study to look at the role of spread of norovirus as a result of staff and intra patient contact would look into contact tracing and monitoring contacts between staff and patients and patient to patient.

This research has outlined the burden in terms of number of outbreaks, staff and patients affected and the number of ward or bay closures. Further understanding of the impacts, in terms of financial implications of norovirus outbreaks, would be extremely useful. This would provide information on any savings that could be made in the event of the introduction of a

vaccine. Furthermore, in future, costs of building new hospitals or upgrading existing facilities to include more single room occupancy buildings might be found to be a cost effective way of preventing or mitigating outbreaks of norovirus.

In the light of the introduction of a vaccine to prevent rotavirus infection in children, norovirus is likely to become a more important cause of diarrhoeal disease in children. Further investigations into the burden of norovirus causing illness in young children would be important.

Further research recommendations

- Detailed outbreak transmission study
    - Collect detailed data on position in ward, timing of illness and location 24-48 hours prior to admission
    - Increased sampling during outbreaks
    - High resolution specimen analysis (P2 domain)
- Contact tracing studies
    - Use of monitors to model the proximity of patients and staff contact during care.
- Further research into the financial burden of norovirus to the NHS
    - Estimate cost benefit of increasing proportion of single occupancy rooms
- Monitor the burden of norovirus disease in children
    - Possible increased impact resulting from rotavirus vaccine introduction

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Appendix 1 Role of authors in constituent papers

Deaths from Norovirus among theelderly, England and Wales

J. Harris, lead author, devised the study with WJ Edmunds and B. Lopman. J Harris carried out the analysis of data and drafted the paper and wrote final draft. WJ Edmunds advised on modelling, B Lopman and DW Brown commented on drafts.

Hospital Admissions Due to Norovirus in Adult and Elderly Patients in England

T. Haustein Lead author devised study with J. Harris and B. Lopman. J. Harris provided data for the study and advised on study methods (modelling) and data analysis and assisted with data analysis. J. Harris wrote the first draft with T. Haustein. B. Lopman and R. Pebody contributed to authorship and revised drafts. R. Pebody advised on use of ONS data.

The development of web-based surveillance provides new insights into the burden of norovirus outbreaks in hospitals in England

J. Harris lead author devised the study with G. Adak. J. Harris gathered and cleaned the data and conducted the analysis with N. Adams. J. Harris wrote the paper and B Lopman, N. L Adams and G.K. Adak provided comments for re-drafting.

Infection control measures for norovirus: a systematic review of outbreaks in semi-enclosed settings

All authors contributed to the design of the study. J. Harris conducted the review and carried out the analysis. J. Harris was lead author and wrote the paper. B. Lopman and S. O'Brien provided comments during drafting.

Does spatial proximity drive norovirus transmission during outbreaks in hospitals?

J. Harris, B Lopman, S. O'Brien all contributed to the design of the study. J. Harris was lead author and principle investigator on the study and devised the method of data collection, liaised with infection control specialists at the hospitals and collected the data for the study.

B. Cooper advised on the statistical analysis and the statistical programming software. J. Harris conducted the statistical analysis with B. Cooper. J. Harris wrote the first draft of the paper. All other authors contributed to re-drafting the paper.

To close or not to close? Analysis of four years data from national surveillance of norovirus outbreaks in hospitals in England

J Harris designed the study and gathered and cleaned the data and conducted the statistical analysis. J Harris was lead author and wrote the paper. All authors contributed to re-drafting the paper.

Appendix 2 Letter from ethics committee and information governance

Salford & Trafford Local Research Ethics Committee
Room 181
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24/Apr08/PC

11 April 2008

Dr Paul Chadwick
Consultant Microbiologist/Clinical Lead
Department of Microbiology
Hope Hospital
Stott Lane
Salford
M6 8HD

Dear Dr Chadwcik

Re:- **'Enhanced Surveillance of Norovirus at Salford Royal NHS Foundation Trust'**

Thank you for your email and clear description of your proposal as set out in the protocol and supporting documents dated 25 March 2008.

The information has been considered by the Chair of Salford and Trafford REC, Dr Mary Tully. She has advised that the project is not one that is required to be ethically reviewed under the terms of the Governance Arrangements for Research Ethics Committees in the UK.

Kind regards

Carol Ebenezer
Committee Co-ordinator

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cc R&D Hope Hospital – Lloyd Gregory

Salford Royal NHS
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Clinical Support Services Group
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17 January 2008

Mr John Harris
Environmental and Enteric Diseases Department
Centre for Infections
Health Protection Agency
61 Colindale Avenue
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Dear Mr Harris

Re: Collaboration on enhanced Norovirus surveillance project

I have discussed the information governance issue with my medical director, Dr Stephen Waldek, and he is happy for yourself and Ben Lopman to have access to anonymised patient data as necessary for the smooth running of this project. He has asked me to remind you that the normal rules around data protection and confidentiality for those of us working in the NHS and Health Protection Agency apply.

I look forward to seeing you soon to discuss the project further.

Kind regards

Yours sincerely

Paul Chadwick
Consultant Microbiologist/Clinical Lead

cc Dr Stephen Waldek